Selective Internal Radiation Therapy for Hepatic Metastases using SIR-Spheres®

March 2002

MSAC application 1034

Assessment report

SIR-Spheres® is a registered trademark of SIRTeX Medical Ltd

© Commonwealth of Australia 2003

ISBN 0 642 82169 0
ISSN (Print) 1443-7120
ISSN (Online) 1443-7139

First printed March 2003

This work is copyright. Apart from any use as permitted under the C*opyright Act 1968,* no part may be reproduced by any process without prior written permission from the Commonwealth available from the Department of Communications, Information Technology and the Arts. Requests and inquiries concerning reproduction and rights should be addressed to the Manager, Copyright Services, Info Access, GPO Box 1920, Canberra ACT 2601.

Electronic copies of the report can be obtained from the Medical Service Advisory Committee's Internet site at:

http://www.msac.gov.au

Hard copies of the report can be obtained from:

The Secretary
Medical Services Advisory Committee
Department of Health and Ageing
Mail Drop 107
GPO Box 9848
Canberra ACT 2601

Enquiries about the content of the report should be directed to the above address.

The Medical Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

This report was prepared by the Medical Services Advisory Committee with the assistance of Kirsten Howard, Epidemiologist and Dr. Martin Stockler, Senior Lecturer from The NHMRC Clinical Trials Centre, University of Sydney, The report was endorsed by the Commonwealth Minister for Health and Ageing on 28 August 2002.

Publication approval number: 3165

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

Contents

Tables

Figures

Executive summary

The Medical Services Advisory Committee (MSAC) has reviewed the use of Selective Internal Radiation Therapy (SIRT) using SIR-Spheres, which is a therapeutic 'device' for the treatment of non-resectable hepatic metastases secondary to colorectal cancer in the absence of extrahepatic metastases and in combination with hepatic arterial chemotherapy or systemic chemotherapy.

The procedure

SIR-Spheres are intended for implantation into malignant liver tumours for the purpose of selectively delivering high doses of ionising radiation to the tumour. This is accomplished by injecting the SIR-Spheres into the hepatic artery. This requires catheterisation of the hepatic artery either via a trans-femoral catheter or a permanently implanted hepatic artery port with catheter.

Following embolisation into the hepatic artery by catheter, SIR-Spheres become concentrated in the microvasculature of liver cancer where they have a local radiotherapeutic effect. Some limited concurrent damage to healthy tissue is caused by radiation that escapes tumour boundaries and from SIR-Spheres that fail to become embedded in tumours. Following decay of the yttrium-90, the inert resin microspheres remain implanted in tissue. As tumours within the liver derive their blood supply almost exclusively from the hepatic artery, the SIR-Spheres are preferentially delivered in greater amounts to the tumour rather than the normal liver parenchyma which is supplied by both the hepatic artery and the portal vein.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the NHMRC Clinical Trials Centre was engaged to conduct a systematic review of literature on Selective Internal Radiation Therapy. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of Selective Internal Radiation Therapy

The Medical Services Advisory Committee (MSAC) has reviewed the use of Selective Internal Radiation Therapy (SIRT) using SIR-Spheres, which is a therapeutic 'device' for the treatment of non-resectable hepatic metastases secondary to colorectal cancer in the

absence of extrahepatic metastases and in combination with hepatic arterial chemotherapy or systemic chemotherapy.

Clinical need

Colorectal cancer is the most common cancer reported to Australian cancer registries. In 1997, there were 11,245 new cases of colorectal cancer reported and 4,678 deaths, accounting for approximately 14.1% of all new cases of cancer (excluding non-melanocytic skin cancer) and 13.8% of cancer related deaths (Australian Institute of Health and Welfare & Australasian Association of Cancer Registries 2000). It is estimated that approximately fifty per cent of patients with colorectal cancer will develop liver metastases within 5 years (Clinical Oncology Society of Australia & Australian Cancer Network 1999; Taylor 1996). In 20-40% of patients, this will be the only (or first) site of failure (Clinical Oncology Society of Australia & Australian Cancer Network 1999).

Safety

Patient safety

The randomised trials provided limited information regarding patient safety. It appears that the addition of SIRT to hepatic arterial chemotherapy may result in additional elevation of hepatic enzymes (alkaline phosphatase), and more nausea and vomiting than hepatic arterial chemotherapy alone. Similarly, the addition of SIRT to systemic chemotherapy appeared to result in more grade 3-4 toxicities (including granulocytopenia and mucositis) than did systemic chemotherapy alone. There was one treatment related death in the combined treatment arm of this trial.

In both trials, patients often experienced abdominal pain after administration of SIR-Spheres which in some cases required narcotic analgesia.

Uncontrolled evidence suggests that administration of SIRT (with SIR-Spheres, or other similar agents) will commonly result in liver enzyme elevations, fatigue and lethargy, anorexia, nausea and/or vomiting and gastrointestinal symptoms. There have been a small number of cases of fatal radiation hepatitis, gastrointestinal ulceration or haemorrhage, and radiation pneumonitis.

Personnel safety

From data reported in a small number of publications, and from information supplied by the applicant, it would appear that the doses of radiation delivered to personnel are reasonably low and are within ranges recommended by the National Occupational Health and Safety Commission (National Occupational Health and Safety Commission 1995). The current NHMRC recommendation (National Health and Medical Research Council 1984) on discharge of patients who have undergone treatment with radioactive substances specifies that discharge should not occur until total activity remaining in the patient has dropped to 1200 MBq. As the dose of yttrium-90 delivered for SIRT is 2-4 GBq, and the half life is >67 hours, the patient may require a 3-4 day hospital stay (not the one day stay as in the randomised controlled trial) before reaching this level.

Effectiveness

There is some evidence that addition of SIRT to hepatic chemotherapy may be more effective than hepatic chemotherapy alone in terms of tumour response in the liver. Depending upon how tumour response was measured, there may have been improved tumour response rates for patients receiving treatment with SIRT. When tumour response was measured by changes in tumour volume, there was a trend favouring SIRT plus hepatic chemotherapy in tumour response. When tumour response was measured by tumour area, patients treated with hepatic chemotherapy plus SIRT had significantly more tumour responses than patients treated with chemotherapy alone.

There is also some evidence to suggest that the addition of SIRT to systemic chemotherapy offered improvements in tumour response as measured by both 'first integrated response' and 'best confirmed response'

The addition of SIRT to hepatic chemotherapy may prolong time to disease progression in the liver. Depending upon how disease progression in the liver was measured, there may have been a benefit for patients receiving SIRT in addition to hepatic chemotherapy. If disease progression was measured by tumour volume, there was a trend favouring SIRT plus hepatic chemotherapy in time to first disease progression in the liver. If disease progression was measured by tumour area, and analysed with a competing risks model, there was a significant difference favouring SIRT plus hepatic chemotherapy ($p=0.033$, Gray's test).

There is insufficient evidence from the trial of hepatic chemotherapy plus SIRT to determine the effect of SIRT on progression-free or overall survival. There was no statistically significant difference in overall or progression-free survival between patients treated with hepatic arterial chemotherapy and those treated with hepatic chemotherapy and SIRT. The trial, however, was insufficiently powered to detect a moderate and clinically important difference in overall and progression-free survival.

The small trial of systemic chemotherapy plus SIRT versus systemic chemotherapy alone suggested that the time to progressive disease in the combination arm was significantly longer; however, overall survival was not reported.

Quality adjusted survival was not reported in either randomised trial. Neither trial was adequately powered to detect a difference in quality of life measures.

Cost effectiveness

It is not possible to give a reliable estimate of cost per life year saved or cost per quality adjusted life year due to the lack of reliable evidence regarding benefit on these outcomes.

Using data from the original analysis, the incremental cost-effectiveness ratio for SIRT is $38,742 per additional patient who has a response in the liver. Depending upon assumptions and the 95% confidence interval of the estimate of benefit, this might plausibly be as low as $17,862 or as high as $232,450 per additional patient who has a response in the liver.

Using data from the blinded re-analysis of tumour response, the incremental cost-effectiveness ratio for SIRT is $39,911 per additional patient who has a response in the liver. Depending upon assumptions and the 95% confidence interval of the estimate of benefit, this might plausibly be as low as $18,696 or as high as $669,017 per additional patient who has a response in the liver.

A comprehensive Australian-based assessment of costs and effects associated with systemic chemotherapy, hepatic arterial chemotherapy and SIRT is needed to provide a basis for a comparison between systemic therapy and hepatic chemotherapy with or without SIRT.

Recommendation

Since there is currently insufficient evidence of effectiveness and cost-effectiveness for Selective Internal Radiation Therapy (SIRT) using SIR-spheres®, MSAC recommended that public funding should not be supported at this time for this procedure.

The data suggests that the treatment is reasonably safe and has anti-tumour activity. However, it is not clear whether this anti-tumour activity translates into a survival or quality of life benefit to the patient.

- The Minister for Health and Ageing accepted this recommendation on 28 August 2002 -

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of Selective Internal Radiation Therapy (SIRT) using SIR-Spheres, which is a therapeutic 'device' for the treatment of non-resectable hepatic metastases secondary to colorectal cancer in the absence of extrahepatic metastases and in combination with hepatic arterial chemotherapy. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for Selective Internal Radiation Therapy using SIR-Spheres for the treatment of non-resectable hepatic metastases secondary to colorectal cancer in the absence of extrahepatic metastases and in combination with hepatic arterial chemotherapy and systemic chemotherapy.

Background

Selective Internal Radiation Therapy

This evaluation was undertaken in response to an application for assessment of Selective Internal Radiotherapy (SIR) using SIR-Spheres, which does not currently have reimbursement under the Australian Medicare Benefits Scheme (Commonwealth Department of Health and Aged Care 2000a).

The Procedure

The following information is from the SIR-Spheres Product Monograph and Physician Labelling (SIRTeX Medical Ltd. 2000a; SIRTeX Medical Ltd. 2000b). SIR-Spheres are beta-emitting yttrium-90 microspheres. They have a diameter of between 20 and 40 microns. Yttrium-90 is a high-energy pure beta-emitting isotope with no primary gamma emission.

SIR-Spheres are intended for implantation into malignant liver tumours for the purpose of selectively delivering high doses of ionising radiation to the tumour. This is accomplished by injecting the SIR-Spheres into the hepatic artery. This requires catheterisation of the hepatic artery either via a trans-femoral catheter or a permanently implanted hepatic artery port with catheter.

Following embolisation into the hepatic artery by catheter, SIR-Spheres become concentrated in the microvasculature of the liver cancer where they have a local radiotherapeutic effect. Some limited concurrent damage to healthy tissue is caused by radiation that escapes tumour boundaries and from SIR-Spheres that fail to become embedded in tumours. Following decay of the yttrium-90, the inert resin microspheres remain implanted in tissue. As tumours within the liver derive their blood supply almost exclusively from the hepatic artery, the SIR-Spheres are preferentially delivered in greater amounts to the tumour rather than the normal liver parenchyma which is supplied by both the hepatic artery and portal vein.

In about 3% of patients with liver tumours there will be significant arteriovenous shunts in the tumour which means that more than 10% of the SIR-Spheres injected into the hepatic artery will pass through the liver and lodge in the lungs. As this may cause radiation damage to the lungs, a nuclear medicine break-through scan must be performed in all patients to assess this possibility. If there is greater than 10% lung shunting, then a reduction in implanted activity should be used. A standard dose of Technetium-99 labelled macroaggregated albumin (MAA) is injected either into the surgically implanted port or via the hepatic artery catheter that is used to perform the pre-treatment hepatic angiogram. The patient is then placed under a gamma camera to define areas of interest (liver and lungs). The ratio of MAA particles that pass through the liver and lodge in the lungs can then be calculated. The percentage of MAA that has escaped through the liver and lodged in the lungs is expressed as a 'lung/liver ratio'. Normally, this is less than 10%. If the lung/liver ratio is more than 10% then the amount of SIR-Spheres delivered to the patient must be reduced, using the dose reduction protocol shown in Table 1.

Table 1 Dose reduction protocol

Lung / Liver Ratio Activity of SIR-Spheres	Dose Reduction Recommendations
< 10%	Deliver full amount of SIR-Spheres
10% to 15%	Reduce amount of SIR-Spheres by 20%
15% to 20%	Reduce amount of SIR-Spheres by 40%
> 20 %	Do not give SIR-Spheres

Intended purpose

SIRT is for the treatment of non-resectable hepatic metastases secondary to colorectal cancer in the absence of extrahepatic metastases and in combination with hepatic arterial chemotherapy. SIRT has also been used to treat primary hepatocellular carcinoma, however, this indication will not be assessed in this review.

Clinical need / burden of disease

Colorectal cancer is the most common cancer reported to Australian cancer registries. In 1997, there were 11,245 new cases of colorectal cancer reported and 4,678 deaths, accounting for approximately 14.1% of all new cases of cancer (excluding non-melanocytic skin cancer) and 13.8% of cancer related deaths (Australian Institute of Health and Welfare & Australasian Association of Cancer Registries 2000).

Premature death from colorectal cancer was responsible for an estimated 31,573 person-years of life lost before the age of 75, second only to lung cancer. Australian age-standardised incidence and mortality rates of colorectal cancer are towards the higher end of the international scale. They are generally slightly lower than those reported for New Zealand and the Czech Republic, and slightly higher than reported for the United States (Australian Institute of Health and Welfare & Australasian Association of Cancer Registries 2000).

It is estimated that approximately fifty per cent of patients with colorectal cancer will develop liver metastases within five years (Clinical Oncology Society of Australia & Australian Cancer Network 1999; Taylor 1996). In 20-40% of patients, this will be the only (or first) site of failure (Clinical Oncology Society of Australia & Australian Cancer Network 1999).

Treatment options for patients who develop hepatic metastases are discussed below.

The number of patients who undergo some treatment for hepatic metastases annually in Australia can be estimated from hospital morbidity data and ICD-9-CM codes (1997-98) and ICD-10-AM codes (1998-99, for New South Wales, Victoria, Australian Capital Territory and Northern Territory only) for primary diagnosis and principal procedures (Commonwealth Department of Health and Aged Care 2000b; Commonwealth Department of Health and Aged Care 2001). There were approximately 5000 separations for one treatment for hepatic metastases in 1997-98 and almost 3000 in New South Wales, Victoria, Australian Capital Territory and Northern Territory in 1998-99. These numbers (shown in Table 2) indicate all episodes of treatment for hepatic metastases

over these time periods, and as such, a single patient may also have undergone multiple treatments. These figures indicate all separations for treatment of hepatic metastases, not only those from patients with colorectal cancer. The number of patients with hepatic metastases from colorectal cancer would therefore only be a proportion of this number.

Table 2 Separations for principal diagnosis of secondary malignant neoplasm of the liver

ICD- code		Condition	Year	Table	Hospital separations
1977	ICD-9	Secondary malignant neoplasm of the liver	1997-98	Table 11	4931
C787	ICD-10*	Secondary malignant neoplasm of the liver	1998-99	Table 11	2822

*ICD-10 only available for NSW, Vic, ACT and NT

ICD-10 procedure codes map to the Medicare Benefits Schedule codes for procedures. MBS code 30400, 'Laparotomy with insertion of portacath for administration of cytotoxic' is the procedure code used for the placement of a reservoir for the delivery of hepatic arterial chemotherapy and SIRT. As only New South Wales, Victoria, Northern Territory and Australian Capital Territory implemented ICD-10-AM from 1 July 1998 the data in Table 3 is likely to be an underestimate of the true number of procedures over this time.

Table 3 Occurrences of principal procedures likely to be associated with hepatic arterial chemotherapy and SIRT

ICD- code		Procedure	Year	Table	Total number of occurrences (Public and Private)
30400-00	ICD-10	Ins VAD w atchmt intra-abdo vesl cath	1999-2000	Table 7	261

(Commonwealth Department of Health and Aged Care 2001)

Existing procedures

The NHMRC Clinical Practice Guidelines for the prevention, early detection and clinical management of colorectal cancer (Clinical Oncology Society of Australia & Australian Cancer Network 1999) provide a summary of treatment options available to patients with hepatic metastases and an indication of the evidence for each option. The NHMRC revised hierarchy of evidence levels is shown in Table 6.

Surgical Resection

There are no controlled trials of liver resection in the treatment of metastatic lesions from colorectal cancer, however, retrospective assessment of the outcome of potentially resectable disease has been examined by several authors. In three studies of patients with apparently resectable lesions, three-year and five-year survival was quite low and ranged from 10-14% and 0-3%, respectively (Bines et al. 1996; Hughes et al. 1988; Wood et al. 1976). In more recent studies of highly selected patients, five-year survival following resection of hepatic metastases has been reported to be between 15 and 50 per cent (Bines et al. 1996).

While early attempts at liver resection had high rates of morbidity and mortality, the mortality of liver resection in non-cirrhotic patients is now considerably less than 5% in

most major units (Clinical Oncology Society of Australia & Australian Cancer Network 1999).

The NHMRC Clinical Practice Guidelines for colorectal cancer concluded that there was Level III evidence that patients with up to four hepatic lesions, and no evidence of extrahepatic disease, should be considered for resection provided that the lesions can safely be removed with an adequate margin (Clinical Oncology Society of Australia & Australian Cancer Network 1999).

Cryotherapy

A recent survey indicated that cryotherapy is generally performed as an open technique, although it has also been performed laparoscopically and percutaneously (Seifert & Morris 1999). Post-operative morbidity appears to be quite limited and mortality has been recorded as 14 in 869 (1.6%).

The comparison of cryotherapy to surgical resection is limited by the fact that few cryotherapy series have five-year survival data. Despite this, there are five-year survivors in many series (Morris et al. 1996; Onik et al. 1991; Onik et al. 1993; Shafir et al. 1996; Weaver et al. 1995; Yeh et al. 1997). There has been one small randomised trial of cryotherapy compared to liver resection, with the two treatments achieving similar results (Korpan 1997).

Alcohol injection

In a controlled trial, alcohol injection for treatment of metastatic colorectal cancer was significantly less effective than laser photocoagulation, due to the limited diffusion of alcohol within fibrous lesions (Amin, Bown, & Less 1993). Other series have described prolonged survival associated with this treatment (Giovanni & Seitz 1994).

Laser photocoagulation

The NHMRC Clinical Practice Guidelines for colorectal cancer indicate that while laser photocoagulation may be an easier method than cryotherapy to use percutaneously, it has to date had quite limited value due to the small volume of tissue destruction around the tip. Clinical data on both tumour marker normalisation and survival are both very limited. One prospective series indicated a 66% 'local tumour control' at six months for lesions less than 2cm in diameter, and a 35% 'local tumour control' in lesions greater than 2cm in diameter (Vogl et al. 1995).

Systemic chemotherapy

Systemic chemotherapy has been given to patients with advanced colorectal cancer with the aim of relieving tumour related symptoms, improving overall quality of life and prolonging survival. The standard systemic treatment for advanced colorectal cancer has become 5-fluorouracil (5FU) plus leucovorin (LV) (Clinical Oncology Society of Australia & Australian Cancer Network 1999). Despite this, a number of meta-analyses have been conducted to determine which regimen is most effective including The Advanced Colorectal Cancer Meta-analysis Project (Advanced Colorectal Cancer Meta-

analysis Project 1992) and The UK National Health Service, Centre for Reviews and Dissemination (National Health Service 1997).

These data (Advanced Colorectal Cancer Meta-analysis Project 1992) indicate a highly significant increase in response rate for the combination of 5-FU plus leucovorin over 5-FU alone (23% vs 10%, $p<0.0001$). However, this improvement in response rate did not translate into any significant survival benefit for patients treated with the combination (11.5 months versus 11 months). The NHMRC Clinical Practice Guidelines (Clinical Oncology Society of Australia & Australian Cancer Network 1999) indicate that two trials not included in these meta-analyses demonstrated significant survival benefits (Loeffler et al. 1992; Petrioli et al. 1995).

The Advanced Colorectal Cancer Meta-analysis Project also found a similar response rate benefit for patients treated with fluorouracil plus methotrexate compared to fluorouracil alone (19% versus 10%, $p<0.001$). Survival was also moderately improved with the combination treatment (10.7 months versus 9.1 months, $p<0.02$)(Advanced Colorectal Cancer Meta-analysis Project 1992).

The NHMRC Clinical Practice Guidelines for the prevention, early detection and management of colorectal cancer (Clinical Oncology Society of Australia & Australian Cancer Network 1999) concluded that:

- There was Level II evidence that 5-FU based chemotherapy prolongs life when compared to best supportive care.
- Timing of commencement of chemotherapy in asymptomatic patients remains unclear; however, one study comparing early and delayed chemotherapy indicated a benefit in patients receiving early treatment (Level II) (Nordic Gastrointestinal Tumour Adjuvant Therapy Group 1992).
- There is Level I evidence that indicates 5-FU plus leucovorin, 5-FU plus methotrexate and continuous infusion 5-FU are all associated with improved response rates over 5-FU alone. Survival benefits may exist, but are small with no clear quality of life benefits over 5-FU alone.
- There is Level II evidence that after failure of 5-FU, second line treatment with irinotecan can prolong life and improve quality of life, compared to best supportive care.

Hepatic Arterial Chemotherapy (HAC)

Hepatic arterial chemotherapy (HAC) involves the administration of chemotherapy agents directly into the liver. Several approaches may be used to deliver the chemotherapeutic agents: via an angiographically placed catheter into the hepatic artery; via surgically implanted infusion ports with an external pump; or via surgically implanted infusion pumps (Vauthey et al. 1996). The NHMRC Clinical Practice Guidelines for colorectal cancer have indicated that HAC has two theoretical advantages over systemic chemotherapy for treatment of liver metastases in patients with no extrahepatic disease:

1. Delivery of hepatic artery chemotherapy leads to a mean hepatic drug concentration approximately 15 times greater than can be achieved with intravenous therapy

(Vauthey et al. 1996). Established liver metastases derive blood supply mainly from the hepatic artery rather than the portal vein.

2. Floxuridine (FUDR) is subject to extensive first pass metabolism, with 94-99% of the administered dose being metabolised by the liver during the first pass. This reduces systemic concentrations and subsequent toxicity and allows large doses to be given with relatively minimal systemic effects (Hohn et al. 1989; Kemeny et al. 1987; Martin et al. 1990; Vauthey et al. 1996). However, it also means that HAC with FUDR is suitable only for patients with no extrahepatic metastases. Patients also need to be sufficiently well to undergo a laparotomy for catheter insertion (Clinical Oncology Society of Australia & Australian Cancer Network 1999).

Safety

While hepatic artery catheterisation is a minimally invasive technique relative to the laparotomy required for port and pump implantation, complications associated with repeated arterial puncture and poor patient acceptance due to frequent catheter migration and the need for hospitalisation and confinement to bed, have limited its use (Vauthey et al. 1996).

Arterial ports combined with an external pump have also been used, and require a laparotomy (and therefore attendant risks) for arterial cannulation, as does the placement of an infusion pump. The main complication with an external port is the 30-42% incidence of catheter or hepatic artery thrombosis, which may necessitate stopping treatment in up to 20% of patients (Vauthey et al. 1996). The surgical implantation of the infusion pump, in comparison to an arterial port with an external pump, has a low complication rate if the procedure is performed by an experienced surgeon who has performed the procedure at least 10 times (Vauthey et al. 1996).

The NHMRC Clinical Practice Guidelines indicate that implantation of a port or infusion pump routinely includes a cholecystectomy to prevent chemical cholecystitis. It is also noted that particular attention should be paid to the ligation of hepatic artery branches which perfuse the stomach, common bile duct and pancreas, to prevent complications such as peptic ulceration resulting from inadvertent perfusion of the stomach with chemotherapeutic agents (Clinical Oncology Society of Australia & Australian Cancer Network 1999).

Technical complications: Vauthey et al (Vauthey et al. 1996) have summarised the technical complications reported to be associated with infusion pump implantation (rather than an arterial port with an external pump):

- An operative mortality rate of less than 1%
- Mechanical problems relating to the catheter, including misplacement, breakage, leakage, kinks or migration (5%)
- Vascular complications such as catheter-artery thrombosis or aneurysm formation (5%)
- Problems associated with implantable pumps (including pump pocket haematoma, seroma or infection or a pump malfunction) (8%)

Toxicity related complications: The NHMRC Clinical Practice Guidelines for colorectal cancer indicate that the toxicities from intrahepatic chemotherapy may include sclerosing cholangitis (10%), which may be fatal in some cases, chemical gastritis or cholecystitis (10%), peptic ulceration (5%), and diarrhoea (5%).

Efficacy

Treatment response and survival: A meta-analysis of six of the seven randomised controlled trials published between 1988 and 1993 comparing HAC with intravenous chemotherapy has shown a significantly higher tumour response rate in favour of HAC (41% compared to 14%). The effect of HAC on survival is less clear – when the data from studies comparing HAC with intravenous chemotherapy were pooled, no significant survival benefit was observed (Meta-analysis Group in Cancer 1996). Many of these studies, although randomised controlled trials, had a sample size that was insufficient to detect any meaningful survival advantage.

Both trials comparing HAC with a control group (managed with supportive care that could include intravenous chemotherapy) indicated a significant survival benefit for HAC (Allen-Mersh, Earlam, & Fordy 1994; Rougier et al. 1997). However, only 20% (Allen-Mersh, Earlam, & Fordy 1994) and 50% (Rougier et al. 1997) of control group patients received any chemotherapy.

The relative benefits of systemic versus hepatic chemotherapy after potentially curative resection of liver metastases are uncertain. A trial of hepatic arterial floxuridine plus systemic 5-fluorouracil (5-FU) plus leucovorin (LV) versus systemic 5-FU/LV was shown to result in improved 2-year hepatic disease-free (90% versus 60%, $p<.001$) and 2-year overall survival rates (86% versus 72%, $p=.03$), but did not show a significant statistical difference in progression-free survival at 2 years (57% versus 42%, $p=.07$) or in overall survival, compared to systemic 5-FU therapy alone (Kemeny et al. 1999). A British trial (Allen-Mersh et al. 2000) using the same regimens as Kemeny et al found no significant difference in overall survival between treatment arms. There was also no significant difference in the proportion of patients on each treatment who died of extrahepatic disease progression. A German trial (Lorenz & Muller 2000) compared hepatic arterial 5-fluorouracil (5-FU) plus leucovorin versus hepatic arterial floxuridine versus systemic 5-FU/LV. This trial found no difference in overall survival between treatment arms. In a pairwise comparison of treatment arms, time to progression was only significantly different for the comparison between hepatic 5-FU/LV versus hepatic floxuridine ($p=.0332$). A significant increase in intrahepatic response (within 6 months) was observed with hepatic 5-FU/LV versus systemic 5-FU/LV (45.0% versus 19.7%, $p=.0099$) and between hepatic floxuridine versus systemic 5-FU/LV (43.2% versus 19.7%, $p=.0195$).

Additional studies are required to resolve these conflicting results on patient survival.

Symptom palliation and quality of life: The effects of HAC on symptom improvement and quality of life is important, particularly in the situation where survival benefits are less clear. Unfortunately, only limited information is available in this area, and only one of the randomised trials comparing HAC with intravenous chemotherapy reported any quality of life comparisons. There was no difference reported in symptoms, performance status or weight gain between the two treatments (Martin et al. 1990).

The NHMRC Clinical Practice Guidelines for the prevention, early detection and management of colorectal cancer (Clinical Oncology Society of Australia & Australian Cancer Network 1999) concluded that there was:

- Level II evidence that hepatic arterial chemotherapy (HAC) has shown survival benefits compared with best supportive care
- Level I evidence that HAC shows higher tumour response rates, but little evidence of a survival advantage over systemic chemotherapy
- Level I evidence that HAC and intravenous chemotherapy should be regarded as acceptable alternative treatments

Comparator

The Supporting Committee decided that hepatic arterial chemotherapy and systemic chemotherapy were possible comparators for this review. For the purposes of the economic evaluation, hepatic arterial chemotherapy is the comparator.

Marketing status of the device

The device used for the delivery of SIRT, SIR-Spheres, is listed with the Australian Therapeutic Goods Administration, with the Listing number of AUST L 63369.

Current reimbursement arrangement

Selective Internal Radiation Therapy using SIR-Spheres is not currently reimbursed, and there is no Medicare Benefits Schedule item number for this procedure.

Approach to assessment

In undertaking this assessment, the literature available on Selective Internal Radiation Therapy (SIRT) and its comparators was reviewed, and a supporting committee was convened to evaluate the evidence surrounding the procedure and provide expert advice.

Review of literature

The medical literature was searched to identify relevant studies and reviews. Searches were conducted in the following databases until 13 February 2001.

- Medline / Pre-Medline
- National Library of Medicine Health Services Research Databases
  - HealthSTAR
  - HSRProj
  - HSTAT
  - HSR Tools
  - DIRLINE
- CINAHL
- Australasian Medical Index (AMI)
- Biological Abstracts
- EBM Reviews – Best Evidence
- Current Contents
- EMBASE
- The Cochrane Library
- ISTAHC Online database (International Society for Technology Assessment in Health Care)
- NHS Centre for Reviews and Dissemination databases
  - DARE (Database of Abstracts and Reviews of Effectiveness)
  - EED (Economic Evaluation Database)
  - HTA (Health Technology Assessment Database)

The search strategy shown in Table 4 was used to identify papers in Medline / Pre-Medline, HealthSTAR, CINAHL, Biological Abstracts and Best Evidence.

Table 4 Search strategy

1	SIRT.mp. [mp=title, abstract, registry number word, mesh subject heading]
2	'selective internal radiotherapy'.mp. [mp=title, abstract, registry number word, mesh subject heading]
3	'selective internal radiation therapy'.mp. [mp=title, abstract, registry number word, mesh subject heading]
4	microspheres.mp. [mp=title, abstract, registry number word, mesh subject heading]
5	yttrium.mp. [mp=title, abstract, registry number word, mesh subject heading]
6	4 and 5
7	1 or 2 or 3 or 6
8	('hep$' or 'liver').mp. [mp=title, abstract, registry number word, mesh subject heading]
9	7 and 8
10	limit 9 to human

A broad search using the terms ['SIRT' OR 'selective internal radiotherapy' OR 'selective internal radiation therapy'] was used for the NHS databases.

Electronic searching also included the Internet sites of the following health technology assessment groups and information sources (Table 5).

Table 5 Health Technology Assessment Organisations

Organisation	Website
International Society for Technology Assessment in Health Care (ISTAHC)	www.istahc.org
International Network of Agencies for Health Technology Assessment (INAHTA)	www.inahta.org
British Columbia Office of Health Technology Assessment (Canada)	www.chspr.ubc.edu.ca/bcohta
Swedish Council on Technology Assessment in Healthcare (Sweden)	www.sbu.se
Oregon Health Resources Commission (US)	www.ohppr.state.or.us/ohrc
Minnesota Department of Health (US)	www.health.state.mn.us
ECRI(US)	www.ecri.org
Canadian Coordinating Office for Health Technology Assessment (Canada)	www.ccohta.ca
Alberta Heritage Foundation for Medical Research (Canada)	www.ahfmr.ca
Veteran's Affairs Research and Development Technology Assessment Program (US)	www.va.gov/resdev
National Library of Medicine Health Service/Technology Assessment text (US)	http://text.nlm.nih.gov
NHS Health Technology Assessment (UK)	www.hta.nhsweb.nhs.uk
Office of Health Technology Assessment Archive (US)	www.wws.princeton.edu/~ota
Institute for Clinical Evaluative Science (Canada)	www.ices.on.ca
Conseil d'Evaluation des Technologies de la Sante du Quebec (Canada)	www.cets.gouv.qc.ca
National Information Centre of Health Services Research and Health Care Technology (US)	www.nlm.nih.gov/nichsr/nichsr.html
Finnish Office for Health Technology Assessment (FinOHTA) (Finland)	www.stakes.fi/finohta/linkit/
Institute Medical Technology Assessment (Netherlands)	www.bmg.eur.nl/imta/
AETS (Spain)	www.isciii.es/unidad/aet/cdoc.htm
Agence Nationale d'Accreditation et d'Evaluation en Sante (France)	www.anaes.fr

The applicant's submission was also reviewed to ensure that all relevant literature was included. This search yielded one additional paper (the journal was not indexed by any of the databases above). Additional published and unpublished data was also provided by

the applicant in their submission and at various times throughout the process of evaluation.

The evidence presented in the selected studies was assessed and classified according to the National Health and Medical Research Council (NHMRC) revised hierarchy of evidence which is shown in Table 6.

Table 6 Designation of levels of evidence

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time series with control group.
III-3	Evidence obtained from comparative studies with historical control, two and more single arm studies or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

Source: NHMRC National Health and Medical Research Council, A guide to the development, implementation and evaluation of clinical practice guidelines. Canberra: NHMRC, 1999.

Eligibility of studies

A total of 77 abstracts were identified in the literature searches, of which 19 were duplicate records retrieved from different databases. The 58 non-duplicate abstracts and one additional paper from the manufacturer's application (total 59) were evaluated to exclude those definitely not eligible. The criteria below were applied to each abstract. The full article was retrieved for 21 abstracts which were either potentially eligible or eligible, or for which there was insufficient information available in the abstract to assess eligibility. The one additional reference that was identified from the manufacturer's application was also examined, as was the one additional reference supplied by the applicant. A total of 23 full papers were evaluated using the same eligibility criteria as used for the abstracts.

Eligibility criteria for studies

1. Studies examining the effectiveness of selective internal radiation therapy using yttrium-90 in treating patients with non-resectable hepatic metastases secondary to colorectal cancer (alone or in combination with another therapy).

   - Studies which examined the use of SIR-Spheres in any other condition eg primary hepatocellular carcinoma, were not included in the assessment of efficacy; however, they have been included in the assessment of safety.
   - Studies which examined the use of a selective internal radiation therapy other than SIR-Spheres for the treatment of liver metastases have been included in the assessment of efficacy and safety.
   - Studies which examined the use of a selective internal radiation therapy other than SIR-Spheres for the treatment of any condition other than liver metastases have been excluded from both efficacy and safety evaluations.

2. English language full journal articles reporting primary data obtained in a clinical setting.

- Reviews, letters, editorials, technical reports and conference abstracts or proceedings were not included.

3. Study design and methods clearly described:

   - Case series of ≥ 10 patients where the authors had attempted to address bias, eg consecutive patients, or where patients could be assumed to be consecutive (that is, all patients within a stated time period).
   - Where it was not possible to determine whether patients were consecutive, papers have been included, but it was noted that patients may not be consecutive.
   - Papers where authors reported on a selected series of patients were not included.
   - Studies with a more powerful design than case series.

4. Or where these inclusion criteria could not be established from the abstract.

The 23 retrieved papers were re-examined using the above criteria, and a further 14 were excluded for the following reasons:

- The paper used a method other than SIR-Spheres to deliver the radiation and patients did not have liver metastases (eligibility criteria 1) (5 papers).
- The paper did not contain sufficient clinical information (either safety or efficacy or both) (eligibility criteria 2) (3 papers).
- Patients had been reported in another, more recent, publication or in an earlier publication which provide more clinical details (eligibility criteria 3) (5 papers).
  - Many authors did not report a date range between which patients were recruited or treated. This made it time consuming and difficult in some cases to determine whether patients had been reported previously in a different publication.
- Less than ten patients (eligibility criteria 3) (1 paper).

A total of nine papers met the eligibility criteria as above. A list of these papers is in Table 7. A list of all papers excluded and the reasons for exclusion is presented in Appendix D.

Additional unpublished clinical data was provided by the applicant for:

- A randomised trial of hepatic arterial chemotherapy (HAC) + SIRT versus HAC alone
- A randomised trial of systemic chemotherapy + SIRT versus systemic chemotherapy alone

It is understood that some of this data has been submitted for publication (SIRTeX Medical Ltd. 2001).

Controlled evidence

It is understood that two papers have been submitted for publication to the Journal of Clinical Oncology (June 2000 and 2001). These data include 74 patients treated as part of the randomised controlled trial of HAC plus SIRT compared to HAC alone and 21 patients treated as part of the randomised controlled trial of systemic chemotherapy plus SIRT compared to systemic chemotherapy alone. A quality assessment of these trials has been conducted using the Method for Evaluating Research Guideline Evidence instrument (MERGE) (Liddle, Williamson, & Irwig 1996). These papers are:

- Gray B., van Hazel G., Hope M., Burton M., Moroz P., Paton G., Anderson J. Randomised trial of SIR-Spheres plus chemotherapy versus chemotherapy alone for treating patients with liver metastases from primary large bowel cancer [Submitted to Journal of Clinical Oncology, June 2000]; and

- Gray B, van Hazel G, Blackwell A, Anderson J, Price D, Moroz P, Bower G, Jackson L. Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer [Submitted to Journal of Clinical Oncology, 2001].

Uncontrolled evidence

The nine case series papers which met the inclusion criteria are listed in Table 7 and the results are summarised in Appendix C. Since there was a control group in only one of these studies, and the studies were small, the statistical significance of the results is likely to be over-emphasised in the reports.

Table 7 List of case series papers Included in review

Author(s)	Title	Publication	Year	N*	Micro-sphere type	Included for
Andrews, J.C., Walker, S.C., Ackermann, R.J., Cotton, L.A., Ensminger, W.D. and Shapiro, B.	Hepatic radioembolization with yttrium-90 containing glass microspheres: preliminary results and clinical follow-up	Journal of Nuclear Medicine 35, 1637-1644	1994	24 (17 LM from CRC)	Glass TheraSphere ®	Efficacy & safety
Blanchard, R.J., Morrow, I.M. and Sutherland, J.B.	Treatment of liver tumors with yttrium-90 microspheres alone	Canadian Association of Radiologists Journal 40, 206-210	1989	16 (15 LM) 20 (control)	Plastic	Safety only
Grady, E.D., McLaren, J., Auda, S.P. and McGinley, P.H.	Combination of internal radiation therapy and hyperthermia to treat liver cancer	Southern Medical Journal 76, 1101-1105.	1983	16 (13 LM)	Resin	Safety only
Gray, B.N., Anderson, J.E., Burton, M.A., van Hazel, G., Codde, J., Morgan, C. and Klemp, P.	Regression of liver metastases following treatment with yttrium-90 microspheres	Australian & New Zealand Journal of Surgery 62, 105-110.	1992	29 (LM)	SIR-Spheres	Efficacy & safety
Gray, B.N., van Hazel, G., Buck, M., Paton, G., Burton, M.A. and Anderson, J.	Treatment of colorectal liver metastases with SIR-Spheres plus chemotherapy	GI Cancer 3, 249-257	2000	71 (LM)	SIR-Spheres	Efficacy & safety
Herba, M.J., Illescas, F.F., Thirlwell, M.P., Boos, G.J., Rosenthall, L., Atri, M. and Bret, P.M	Hepatic malignancies: improved treatment with intraarterial Y-90	Radiology 169, 311-314	1988	15 (12 LM from CRC)	Glass TheraSphere ®	Efficacy & safety
Ho, S., Lau, W.Y., Leung, T.W., Chan, M., Johnson, P.J. and Li, A.K	Clinical evaluation of the partition model for estimating radiation doses from yttrium-90 microspheres in the treatment of hepatic cancer	European Journal of Nuclear Medicine 24, 293-298	1997	100 (6 LM)	SIR-Spheres	Safety only
Lau, W.Y., Ho, S., Leung, T.W., Chan, M., Ho, R., Johnson, P.J. and Li, A.K.	Selective internal radiation therapy for nonresectable hepatocellular carcinoma with intraarterial infusion of 90yttrium microspheres	International Journal of Radiation Oncology, Biology, Physics 40, 583-592	1998	71 (all PLC)	SIR-Spheres	Safety only
Stubbs, R.S., Cannan, R.J., Mitchell, A.W.	Selective internal radiation therapy with 90yttrium microspheres for extensive colorectal liver metastases	Journal of Gastrointestinal Surgery 5 (3), 294-302	2001	50 (CRC)	SIR-Spheres	Efficacy & safety

* LM – liver metastases, CRC - colorectal cancer, PLC - primary liver cancer
TheraSphere® is a registered trademark of MDS Nordion

The evidence for the efficacy and safety of SIRT is therefore based on two unpublished and small randomised controlled trials (level II evidence): one comparing hepatic arterial infusion with and without SIRT and the other comparing systemic chemotherapy with and without SIRT. These data are supplemented by a number of uncontrolled case series reports.

Expert advice

A supporting committee with expertise in clinical oncology, surgery and radiation medicine was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the supporting committee is provided at Appendix B.

Results of assessment

Two randomised controlled trials of selective internal radiation therapy in the treatment of hepatic metastases from colorectal cancer were identified. Trials will be discussed individually in this section and a full quality assessment of both trials using the MERGE instrument (Liddle, Williamson, & Irwig 1996) is reported in Appendix C.

Methodological assessment of randomised trials

Hepatic Arterial Chemotherapy (HAC) + SIRT

This trial was included in the MSAC application as a trial report (a publication from this trial has been submitted to the Journal of Clinical Oncology, June 2000) and was conducted by the applicant. The trial compared hepatic arterial chemotherapy (HAC) with hepatic arterial chemotherapy plus SIRT using SIR-Spheres. The HAC was a regimen of floxuridine in ongoing 12 day cycles of continuous infusion, repeated at four weekly intervals.

The data presented in this report are based on all patients (eligible and ineligible).

Randomisation, allocation concealment and blinding

The randomisation method used in this trial is not reported in either the trial report or the submitted publication. The trial protocol was requested from the applicant and indicates that the randomisation method used was a blind coded envelope in a blocked randomisation format.

Sample size and power

There is only a limited discussion of power and sample size in the trial report. The protocol provides some additional information. The trial was designed to enter 95 patients over three years. The original trial protocol indicated that survival was used to calculate sample size and power. A total of 95 patients would allow a detection of a 30% improvement in median survival (assuming 50% at six months) with a power of 90% (one sided test with a 5% significance). The trial entered 74 patients over six years before being stopped as patients were being referred specifically for SIRT treatment and were refusing randomisation. An amendment to the protocol after recruitment was stopped indicates that tumour response had been changed to the primary outcome measure and states that 74 patients would allow detection of increases as follows:

- In response rate from 20% to 55% (difference of 35%) with 80% power and 95% confidence;
- In time to progression in the liver of 32% with 80% power using a 95% confidence level; and
- In survival of 30% absolute increase with 90% power using a 90% confidence level.

Efficacy Outcomes

The primary and secondary efficacy outcomes for this trial are not clearly described in either the trial report or the publication. The original trial protocol indicates that the primary objectives were to compare survival and quality of life between treatment arms. Secondary objectives were to compare toxicity and objective tumour response rates of the two treatment regimens.

A protocol amendment was made after trial accrual stopped and indicates that the primary objectives of the trial were now to compare treatment regimens with respect to:

1) objective tumour response rates;

2) time to disease progression in the liver;

3) overall survival;

4) toxicity of the two treatment regimens; and

5) quality of life.

In addition to the outcomes above, which were specified in the protocol, a number of other outcomes have been reported in the clinical trial report which were not pre-specified in the protocol, including duration of protocol chemotherapy, duration of non-protocol chemotherapy, time to treatment failure, duration of any response in the liver, time to first progressive disease at any site, size of tumour regression and time to first response.

Outcome measurement

Tumour response was measured in a number of ways: 1) tumour volume, 2) serum carcinoembryonic antigen (CEA) levels and 3) tumour area (see comments below: 'Is it effective?'). The authors have indicated a preference for the use of tumour volumes over tumour areas in the assessment of response as 'there are potential difficulties in using tumour areas from cross sectional diameters to calculate response to treatment' (Gray et al. 2000a; SIRTeX Medical Ltd. 2000c).

The trial report indicates that patients underwent computed tomography (CT) scans of the liver before randomisation and at three monthly intervals. Serum CEA levels were measured monthly.

Tumour volume: The trial report states that 'all CT scans on all patients were independently evaluated by two medical practitioners not associated with the trial… Both medical practitioners were unaware of the treatment given to any patient and were unaware of the results of each other's measurements. …if any recording of a tumour volume varied by more than 10% from the mean of the two measurements, then the scans were independently traced by a third medical practitioner (BG). Tumour volume was then taken as the mean of the two closest values.' It should be noted that the third medical practitioner was the primary investigator and was not blinded to the patient's treatment allocation.

Tumour Area: Response as defined by tumour area was evaluated by only one individual (the primary investigator - BG) and was therefore not evaluated blindly. The trial report

indicates that 'tumour areas were taken from measurements of all clearly measurable index lesions that could be tracked on serial CT scans.' The possibility of bias must be considered in such a situation.

Serum CEA changes: The assay for CEA changed during the trial and the report indicates that 'appropriate reference ranges were used to calculate response'. However, the report does not indicate what reference ranges were used, the validity of these ranges, or whether reference ranges changed over the course of the trial.

Definition of response

Tumour response

A partial response (PR) was defined as 'an objectively measured decrease in tumour size by 50% on two or more successive CT scans not less than four weeks apart, after randomisation and before evidence of progressive disease in the liver'.

A complete response (CR) was defined as 'the disappearance of all tumour on two successive CT scans not less than four weeks apart, after randomisation and before evidence of progressive disease in the liver.'

A response was deemed to have 'occurred only if non-protocol chemotherapy had not commenced, except when the non-protocol chemotherapy was systemic 5-FU substituted for protocol chemotherapy due solely to the development of extrahepatic metastases'.

A response as measured by CEA was defined as a decrease in CEA by 50% or more on any occasion after randomisation, before evidence of progressive disease as measured by CEA and before the start of other treatment. The CEA levels used to define response categories (complete response, partial response and progressive disease) are not defined by the authors.

Time to disease progression (in the liver and at any site)

Time to first progressive disease is defined as the time from randomisation to the time at which progressive disease was recorded.

Progressive disease (PD) in the liver was measured using tumour volume, tumour area and CEA and was defined as follows:

- An increase in tumour volume by 25% over the nadir reading for tumour volume as measured on serial CT scans, or in the development of new lesions.

- An increase in tumour area by 25% over the nadir as measured on serial CT scans, or development of new lesions.

- For patients in whom serum CEA was elevated at the time of starting protocol treatment, PD was defined as an increase in serum CEA by more than 25% over the nadir reading for CEA, providing that the CEA is outside the normal reference range.

- For patients in whom there was no objective measure of progression as above, PD is defined as the date of death (if dead) or date of last follow-up (if alive).

Progressive disease at any site was determined by using two measures:

- Increase in CEA.

- Other CT scan evidence of progression in the liver or the appearance of new lesions outside the liver using any imaging technique or clinical or histological evidence, whichever came first.

Patient characteristics

Seventy-four patients were randomised over a six year period to receive either hepatic arterial chemotherapy (HAC) or HAC + SIRT. Four patients were deemed ineligible after randomisation (three in the SIRT + HAC arm and one in the HAC alone arm).

Table 8 describes patient characteristics of both treatment arms and includes data on all patients (eligible and ineligible).

Table 8 Patient characteristics (all patients) for HAC + SIRT vs HAC alone trial

Characteristics	HAC only	HAC + SIRT
Total number	35	39
Male	26	31
Female	9	8
Age (Mean ± SD)	61.64 ± 9.61	58.7 ± 9.39
Regional Lymph node involvement		
Yes	25	27
No	10	12
Size of Liver Metastases		
<25%	24	26
25-50%	9	9
>50%	2	4
Previous liver metastases treatment		
Yes	5	5
No	30	34
Time from diagnosis of metastases to randomisation (days)		
Mean ± SD	132 ± 241	134 ± 253
Median	51	56

Systemic Chemotherapy + SIRT

This trial was conducted by the applicant and data was provided to the Supporting Committee in October 2001. The applicant has indicated that this data has been submitted for publication to the Journal of Clinical Oncology, 2001.

Twenty-one patients were randomised to receive either systemic chemotherapy plus SIRT or systemic chemotherapy alone. Systemic chemotherapy consisted of 5-fluoruracil

425mg/m^2/day plus leucovorin 20mg/m^2/day for five consecutive days, repeated at four weekly intervals. Chemotherapy was continued in both patient groups until evidence of unacceptable toxicity, patient request or disease progression. Patients randomised to the combination arm had SIR-Spheres administered into the hepatic artery via a trans-femoral catheter on the 3rd or 4th day of the second cycle of chemotherapy. The first five patients received a standard dose of 2.5 GBq of yttrium-90 activity. Doses in subsequent patients were administered according to the following formula, as one patient developed radiation hepatitis at the 2.5 GBq dose.

Dose (GBq) = (Body surface area (m^2)-0.2) + (% tumour involvement/100)

Once protocol treatment ceased, further cancer treatment was allowed, including non-protocol chemotherapy. Other supportive treatment was also allowed.

Randomisation, allocation concealment and blinding

Patient registration and randomisation was made by telephoning an independent site which randomised patients using a computer based program. Patients were entered into the study from three Australian hospitals and were stratified prior to randomisation by institution, presence or absence of extrahepatic metastases and extent of liver involvement (<25% or >25%).

Sample size and power

There is no discussion of power and required sample size for this trial. The report simply states that the trial was designed to recruit 18 patients, and closed after 21 patients.

Efficacy Outcomes

The trial report indicates that the phase 2 study was undertaken to compare toxicity and response in the treatment arms.

Outcome measurement

Response was measured using the RECIST criteria (Response Evaluation Criteria in Solid Tumors) (Therasse et al. 2000) (Appendix F). All serial CT scans were read by a blinded, independent person not associated with the trial. Response was reported as 'first integrated response' and 'best confirmed response'.

Toxicity was recorded on all patients 'using standard Union Internationale Contre le Cancer (UICC) recommendations for grading of acute and subacute toxicity criteria'.

Quality of life was measured at randomisation, and then at three monthly intervals using the 23 point Functional Living Index – Cancer (FLIC) questionnaire. Clinicians also reported an assessment of the patients' well-being at the same intervals using the Spitzer index.

Patient characteristics

Twenty-one patients were randomised in this trial, ten to receive only systemic chemotherapy and eleven to receive systemic chemotherapy plus SIRT.

Table 9 describes patient characteristics of both treatment arms.

Table 9 Patient characteristics (all patients) for chemotherapy +SIRT vs chemotherapy alone trial

Characteristics	Chemotherapy only	Chemotherapy + SIRT
Total number	10	11
Male	8	10
Female	2	1
Mean age	65	64
Extrahepatic metastases	3	2
Histologic differentiation of primary bowel cancer:		
Poor	2	1
Moderate	6	10
Well	2	0
Size of Liver Metastases		
<25%	7	8
>25%	3	3

Small patient numbers in this trial may limit the generalisability of conclusions. Extreme percentages should also be viewed with caution, due to the small patient numbers.

Is it safe?

Controlled evidence

Patient Safety

Hepatic Arterial Chemotherapy + SIRT

The protocol indicates that serial measurements to determine treatment response, toxicity and clinical management were performed. Monthly evaluations of full blood examinations, platelet counts, liver function tests and CEA were conducted. Originally, the protocol required chest x-rays and CT scans of the liver to be conducted every three months until there was evidence of disease progression. This was later amended to include only CT scans of the liver.

Table 10 summarises the adverse effect data reported from the randomised controlled trial for all patients (eligible and ineligible) (SIRTeX Medical Ltd. 2000c). Although the protocol indicated that monthly evaluations of haematological and hepatic parameters were conducted, the applicant has indicated that no additional adverse event information is available.

Table 10 Adverse effects reported in randomised controlled trial (Number of events for duration of protocol treatment)

Parameter	Hb				Bilirubin				AST				Alk phosphatase				Nausea/vomiting				Diarrhoea				Total	Total grade 3/4
Toxicity Grade[1]	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4		
Chemotherapy (n=35)	3	1	1		6	1			77	34	14	2	62	30	6		3	2	2		5	1	1		251	26
SIRT + chemo (n=39)	4	1			2		1		94	18	5	2	142	57	14		9	6	1		2	1			357	22

Note: Hb – haemoglobin; AST - aspartate amino-transferase; Alk - Alkaline

Although not tabulated as part of the adverse events, the trial report indicated that many patients experienced discomfort in the upper abdomen soon after the implantation of SIR-Spheres, with some patients requiring narcotic analgesia for the pain. Additional information requested from the applicant has indicated that one patient also experienced grade 2 pain on implant of SIRT. The following information concerning patient safety was included in the submitted publication (Gray et al. 2000a), with one patient developing pancreatitis after SIRT plus HAC, which settled within three days, but nonetheless caused an exacerbation of diabetes.

The application also provided some details of Serious Adverse Events (SAEs) that occurred during protocol treatment (Table 11). An SAE was defined by the authors as any event which resulted in hospitalisation, that was potentially or actually life threatening, or caused death.

[1] The toxicity of treatments was assessed using standard UICC criteria.

Table 11 Serious adverse events during protocol treatment

Event	Chemotherapy arm (n=35)	SIRT + chemotherapy arm (n=39)
Removal of port for any reason	1	2
Re-siting of port for any reason	1	6
Infection or blockage of port not leading to removal or re-siting	4	2
Other port related events	3	0
Fever of uncertain origin	2	1
GI symptoms of uncertain origin	2	1
Surgical complications	1	1
Total	**14**	**13**

GI - gastrointestinal

The applicant has also provided a summary of the potentially treatment-related adverse events (Table 12).

Table 12 Potentially treatment-related adverse events

SIRT + chemotherapy				
Pt ID	**Adverse event**	**Suspected Cause**	**Grade**	**Time since treatment start**
9	Fever	FUDR	2	1mo
	Fever	FUDR	2	2mo
15	Upper chondrial & back pain due to gastritis	FUDR	1	1mo
22	Nausea & vomiting	FUDR	2	1mo
	Indigestion	FUDR	2	2mo
25	Gastric reflux/indigestion	FUDR	2	2mo
30	Nausea, vomiting, pain	^{90}Y	2	Start
	Nausea & vomiting	FUDR	1	1 mo
34	Diarrhoea	FUDR	2	2mo
36	Nausea	^{90}Y/ FUDR	1	2wk
	Pancreatitis	^{90}Y/ FUDR	3	6wk
37	Nausea & vomiting	FUDR	3	2wk
47	Rt hypochondrial pain	FUDR	1	1mo
	Pain	FUDR	2	2mo
50	Rt hypochondrial pain	FUDR	1	2mo
	Indigestion	FUDR	1	2mo
65	Nausea	^{90}Y/ FUDR	1	1mo

Chemotherapy				
Pt ID No.	**Adverse event**	**Suspected Cause**	**Grade**	**Time since treatment start**
69	Epigastric pain, Chest pain (Losec)	FUDR	1	2mo
43	Abdominal discomfort	FUDR	1	2mo
	Indigestion	FUDR	1	2mo
38	Epigastric discomfort	FUDR	1	Start
17	Gastritis	FUDR	1	2wk
	Nausea	FUDR	2	1mo
3	Nausea & vomiting	FUDR	1	1mo
	Diarrhoea	FUDR	2	1mo
	Abdominal discomfort	FUDR	1	1mo
	Diarrhoea	FUDR	1	2mo

FUDR – floxuridine; ^{90}Y - yttrium-90; mo – months; wk - weeks

Note: FUDR – floxuridine, ^{90}Y - yttrium-90, mo – months, wk - weeks

Systemic Chemotherapy + SIRT

There was one treatment-related death in this trial; a patient treated with systemic chemotherapy and SIRT. The patient received four cycles of chemotherapy and experienced neutropenia on each occasion. After the fourth cycle the patient died from sepsis associated with the neutropenia.

Additional adverse effects (grade 3-4 only) are tabulated below (Table 13).

Table 13 Grade 3 and 4 toxicities experienced during treatment

Event	Number of events in Chemotherapy arm (n=10)	Number of events in SIRT + chemotherapy arm (n=11)
Granulocytopenia	0	3
Nausea, vomiting	1	1
Mucositis	1	4
Gastritis	1	1
Diarrhoea	1	2
Anorexia	1	0
Radiation induced cirrhosis	0	1
Liver abscess	0	1
Total number of Grade 3-4 events	**5**	**13**
Treatment related deaths	**0**	**1**

In addition, four patients treated with SIRT + chemotherapy developed abdominal pain at the time of injection of SIR-Spheres that required treatment with narcotic analgesia.

Personnel safety

The controlled evidence provided for this application provided no information regarding operator or personnel safety.

Uncontrolled evidence

Patient Safety

Generally, side effects were not well reported in the case series. Extreme percentages should be viewed with caution because of the small patient numbers in many series. Documented adverse effects from included case series are tabulated below (Table 14).

Table 14 Summary of adverse effects from case series

		Liver enzyme elevations	Radiation hepatitis - fatal	Fever	Fatigue / lethargy	Anorexia	Abdominal pain / discomfort	Nausea and/or vomiting	Gastritis / other GI symptoms	GI Ulceration	GI ulceration requiring surgery	GI tract haemorrhage – non-fatal	Biliary sclerosis	Bilirubin fluctuations	WBC fluctuations	Radiation pneumonitis
Study	**N**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**
(Andrews et al. 1994a)	24	100		17	75				17						0	0
(Blanchard, Morrow, & Sutherland 1989b)	16	19				31		31	19	19	6					
(Grady et al. 1983c)	16		6							6						
(Gray et al. 1992f)	No safety data reported															
(Gray et al. 2000b)	71		1				Common	Common					0			
(Herba et al. 1988h)	15	93			100					20		7		13	7	
(Ho et al. 1997i)	100															5
(Lau et al. 1998j)	71			14			17	17							0	0
(Stubbs, Cannan, & Mitchell 2001)	50				100	100	28	NR		12		3				0

Personnel Safety

One of the publications assessed for eligibility contains comments regarding personnel safety (Shepherd et al. 1992). The authors indicated that radiation exposure to personnel was limited to less than 0.2µSv per administration. When the patient returned to the ward after treatment, the dose rate at 1m from the patient was less than 2µSv/h/GBq administered. At the skin anterior to the liver, the dose rate was 35µSv/h/GBq injected.

In Australia, individual State regulations require that the effective dose to each exposed worker is less than 20mSv per year (averaged over a period of five consecutive calendar years) and that the effective dose limit in a single year is 50mSv, as defined by the NHMRC in it's Radiation Health Series (National Occupational Health and Safety Commission 1995). The applicant has indicated that SIR-Spheres are shielded with lead and Perspex throughout production, transport and delivery, and has provided sample radiation dose reports for selected staff members. During a period of six months during which 15 patients were treated with SIR-Spheres, the applicant has indicated that each staff member received less than 0.15mSv per two month period. A recent Australian review has suggested that the average effective background dose received by the Australian population is approximately 1.5mSv per year (Webb, Solomon, & Thomson 1999).

As beta-emitting radioisotopes have the potential to deliver high doses of radiation to objects close to the source, the whole body exposure rates reported above would be expected to be low. The applicant has provided additional information based on doses measured on finger badges, as below (Table 15).

Table 15 Radiation doses from finger badges (January 1 2000 to December 31 2000)

Wearer	Dose (mSv)	Times worn	Average finger dose per implant (mSv)
Technologist (drawing up)	<0.02	5	0.004
Waste technician	0.82	8	0.1
Administering physician	1.67	2	0.84
Interventional radiologist	<0.02	2	<0.01

Another important consideration is that of residual radiation present on discharge of patients from a hospital facility. The current NHMRC recommendation (National Health and Medical Research Council 1984) on discharge of patients who have undergone treatment with radioactive substances specifies that discharge should not occur until total activity remaining in the patient has dropped to 1200 MBq. As the dose of yttrium delivered for SIRT is 2-4 GBq, and the half life is >67 hours, the patient may require a 3-4 day hospital stay before reaching this level (not the one day stay as in the randomised controlled trial). This may have implications for the total cost of delivery of SIRT (see Section 'What are the economic considerations?'). It is likely that these discharge recommendations will be revised in the near future.

Conclusions

- Based on the randomised trial of HAC plus SIRT versus HAC alone, it appears that the addition of SIRT to hepatic arterial chemotherapy may result in

additional elevation of hepatic enzymes (alkaline phosphatase), and more nausea and vomiting than hepatic arterial chemotherapy alone.

- Similarly, the addition of SIRT to systemic chemotherapy appeared to result in more grade 3-4 toxicities (including granulocytopenia and mucositis) than did systemic chemotherapy alone. There was one treatment-related death in the combined treatment arm of this trial (sepsis).

- Patients in both randomised trials often experienced abdominal pain after administration of SIR-Spheres and in some cases required narcotic analgesia.

- Uncontrolled evidence suggests that administration of selective internal radiation therapy (with SIR-Spheres, or other similar agents) will commonly result in liver enzyme elevations, fatigue and lethargy, anorexia, nausea and/or vomiting and gastrointestinal symptoms.

- There have been a small number of cases of fatal radiation hepatitis, gastrointestinal ulceration or haemorrhage, and radiation pneumonitis.

- It would appear that the doses of radiation delivered to personnel are reasonably low and are within ranges recommended by the National Occupational Health and Safety Commission (National Occupational Health and Safety Commission 1995).

- To comply with the current NHMRC recommendation (National Health and Medical Research Council 1984) on discharge of patients who have undergone treatment with radioactive substances which specifies that discharge should not occur until total activity remaining in the patient has dropped to 1200 MBq, the patient may require a 3-4 day hospital stay after treatment with SIR-Spheres. It is likely that this discharge recommendation will be revised in the near future.

Is it effective?

The Supporting Committee agreed that the following hierarchy of efficacy endpoints should be used in the evaluation of data.

1. Quality adjusted survival (quality adjusted life years - QALYs)
2. Overall survival (ie not adjusted for quality of life)
3. Progression-free survival
4. Hepatic progression-free survival
5. Tumour response rate
    - The randomised controlled trial measured tumour response by a number of methods: change in tumour area, tumour volume and tumour markers (CEA). The supporting committee agreed that tumour area was the conventional method for determining tumour response, and tumour volume and CEA were both considered unconventional methods.

Controlled evidence

As detailed previously (page 17) the clinical trial of HAC plus SIR-Spheres verses HAC alone measured a large number of endpoints, as specified in the protocol, and reported on many more in the trial report.

This section provides data on the efficacy endpoints for both trials that have been determined to be most relevant by the Supporting Committee, as above.

Quality Adjusted Survival

Hepatic Arterial Chemotherapy + SIRT

The trial did not report quality adjusted survival in these patients. The trial report indicates that an attempt was made to determine patient quality of life by using a linear analogue self assessment scale of 11 questions. The trial was not powered to detect a difference in any quality of life measures. The applicant did not use a validated quality of life measure that could provide a utility value which could then be incorporated into a QALY calculation. With the exception of a brief paragraph indicating that 'the patients' perception of their general status was not substantially different between the two study arms', little data on quality of life is provided.

Systemic Chemotherapy + SIRT

The trial did not report quality adjusted survival. Quality of life (QOL) was assessed using both a patient based assessment (FLIC) and a physician based assessment (Spitzer index). Changes from baseline patient related quality of life for the first three months of treatment were analysed using a t-test, and were found to be almost identical in both treatment groups ($p=0.96$). This was also the case for physician rated QOL ($p=0.98$).

Overall survival

Hepatic Arterial Chemotherapy + SIRT

The trial report indicated that there was no statistically significant difference in survival between the two treatment arms. The median survival in the HAC only arm was 477 days, and the median survival in the HAC + SIRT arm was 501 days (detailed in Table 16).

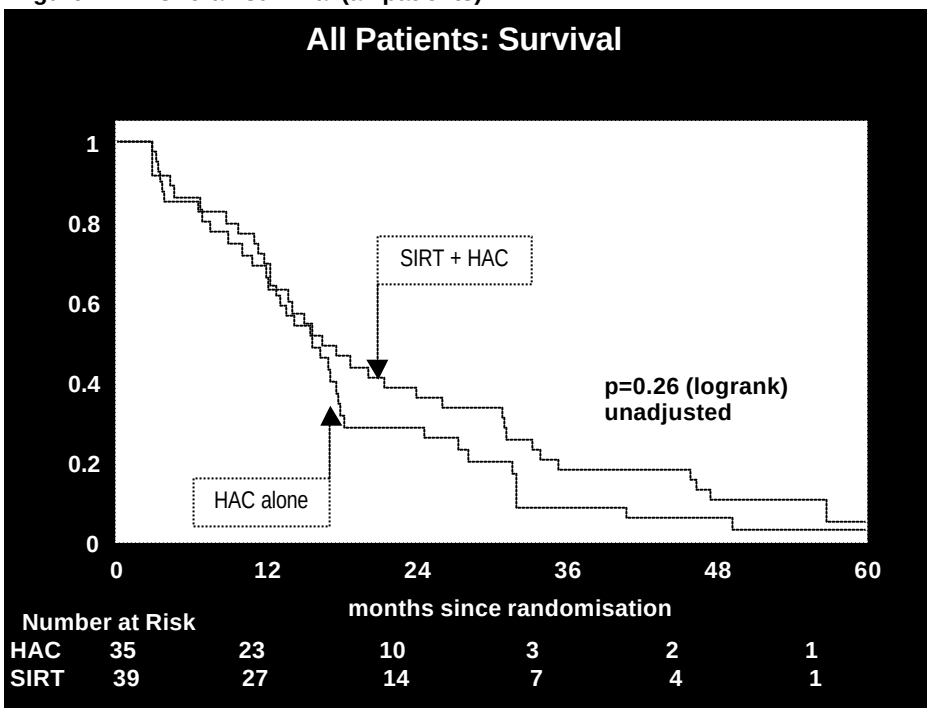
Table 16 Survival - All patients (from trial report)

	HAC alone	HAC + SIRT
N	35	39
Mean survival ± SD (days)	550 ± 389	684 ± 555
Median survival (days)	477	501

Comparison between groups: logrank test p=0.26

The Kaplan Meier curve in Figure 1 indicates overall survival for all patients.

Figure 1 Overall survival (all patients)



Systemic Chemotherapy + SIRT

Overall survival was not reported in this trial.

Progression-free survival (time to disease progression at any site)

Hepatic Arterial Chemotherapy + SIRT

Time to first progressive disease at any site appeared to be measured by the applicant by using: 1) CEA levels; and 2) CT (which included CT evidence of progression in the liver or the appearance of new lesions outside the liver using any imaging technique, whichever came first). Results are shown in Table 17.

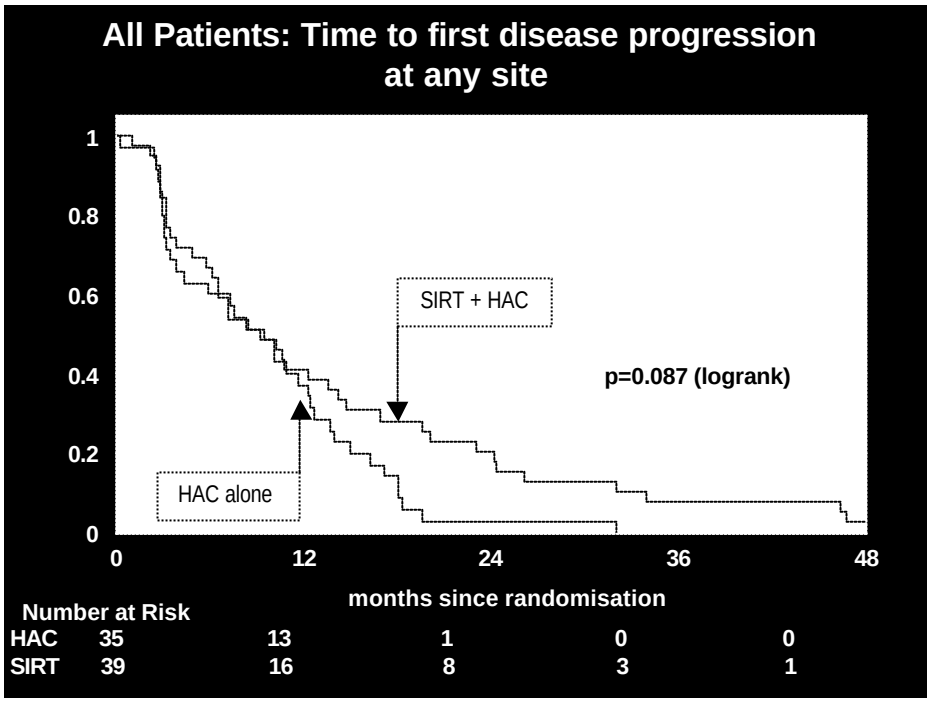
Table 17 Time to disease progression at any site - All patients (from trial report)

	HAC alone	HAC + SIRT
N	35	39
Mean survival ± SD (days)	291±212	442±504
Median survival (days)	287	295

Comparison between groups: logrank test p=0.094

The Kaplan Meier curve below (Figure 2) indicates time to first disease progression at any site (progression-free survival) for all patients. The applicant has indicated that this curve has been constructed based on CT defined progression.

Figure 2 Time to first disease progression at any site (all patients)



Systemic Chemotherapy + SIRT

Although the report does not specify whether the outcome of 'time to disease progression' was at any site, or in the liver only, it is assumed to mean the former. The authors report that as of 10 September 2001, eight of 10 patients in the control arm and four of 11 patients in the experimental arm have recorded progressive disease. The duration of follow-up of these patients is not stated. At this time point, the time to progressive disease was significantly longer for patients treated with chemotherapy plus SIRT (Table 18).

Table 18 Time to progressive disease (as at 10 September 2001)

Treatment arm	Median (months)
Chemotherapy alone	3.4
Chemotherapy plus SIRT	15.6

Comparison between groups p<0.0005

Hepatic progression-free survival (time to disease progression in the liver)

Hepatic Arterial Chemotherapy + SIRT

The trial report indicates that time to disease progression in the liver was measured in a number of ways:

1. Tumour volume (blinded);
2. Tumour area (unblinded); and
3. CEA levels (although no data is presented on this measure).

Median time to disease progression in the liver (as measured by tumour volume) was 230 days for patients treated with hepatic arterial chemotherapy alone and 324 days for patients receiving HAC plus SIRT (Table 19).

Table 19 Time to first disease progression in the liver (tumour volume - All patients)

	HAC alone	HAC + SIRT
N	35	39
Mean ± SD (days)	306 ±327	482 ±505
Median (days)	230	324

Difference between groups (logrank test) p=0.08 (all patients)

Median time to disease progression in the liver (as measured by tumour area) was 287 days for patients treated with chemotherapy alone and 469 days for patients treated with hepatic arterial chemotherapy plus SIRT (p=0.001) (Table 20).

Table 20 Time to first disease progression in the liver (tumour area - All patients)

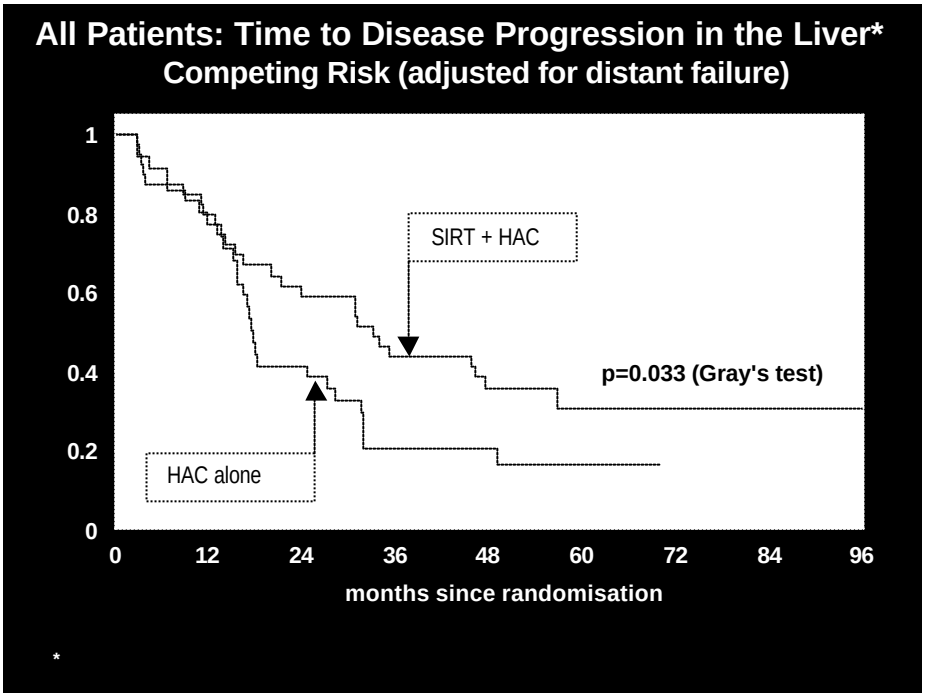
	HAC alone	HAC + SIRT
N	35	39
Mean ± SD (days)	300±211	563±509
Median (days)	287	469

Difference between groups (logrank test) p=0.001

An analysis of 'time to first relapse in the liver only' has been performed using a competing risks analysis due to the fact that once patients fail distantly (outside the liver) their management alters (commencement of systematic treatment etc) which potentially alters their subsequent disease history. Thus, failing in sites outside the liver may be viewed as competing for the event of local failure. A competing risks analysis using the method of Gray (1988), stratified according to disease extent (a randomisation strata in the original study) has been performed. The analysis does not lend itself to Kaplan-Meier type curves but cumulative incidence curves. To help facilitate comparisons, the curves have been transformed to start at one (rather than 0) and decrease (rather than increase) (Figure 3). The applicant has indicated that data based on tumour areas has been used to calculate these cumulative incidence curves.

It should be noted that tumour volume was measured independently by two readers who were blinded to treatment allocation of the patients and were independent to the trial. Tumour area, however, was measured by only one reader (the primary investigator) and was not evaluated blind to treatment allocation or any other clinical data. The potential for reporting bias in such a situation should be noted. To address the issue of possible reporting bias, the applicant has reanalysed tumour response data in a blinded fashion, and this information is reported on the following pages.

Figure 3 Time to disease progression in the liver adjusted for distant failure (for all patients, measured by tumour area and stratified according to disease extent)



*Adjusted for disease extent

Systemic Chemotherapy + SIRT

Time to disease progression in the liver was not reported in this trial, as mentioned earlier in this section.

Tumour response rates

Hepatic Arterial Chemotherapy + SIRT

The applicant has measured tumour response using three methods:

1. Tumour volume (blinded);
2. Tumour area (unblinded); and
3. CEA.

For completeness, results of all measures are presented; however, it should be noted that the supporting committee indicated that tumour area was usually the standard measure. Tables 21, 22 and 23 provide information as to how many patients achieved a complete response (CR), partial response (PR), no change (NC), or progressive disease (PD). The

category of 'other' refers to patients with only a baseline and no follow-up imaging or patients who were considered unmeasurable or unevaluable. In the case of CEA data, patients who had CEA levels in the normal range at baseline could not be evaluated.

Table 21 Tumour response as measured by tumour volume (all patients)

Response	CR	PR	NC	PD	Other	Total
HAC alone	1	7	12	9	6	35
HAC + SIRT	2	16	12	6	3	39

CR - complete response, PR - partial response, NC - no change, PD - progressive disease
Difference between groups (Kruskal-Wallis test for categories CR, PR, NC, and PD) p=0.064

Table 22 Tumour response as measured by tumour area (all patients)

Response	CR	PR	NC	PD	Other	Total
HAC alone	0	6	13	8	8	35
HAC + SIRT	2	14	15	4	4	39

CR - complete response, PR - partial response, NC - no change, PD - progressive disease
Difference between groups (Kruskal-Wallis test for categories CR, PR, NC, and PD) p=0.023

Table 23 Tumour response as measured by CEA (all patients)

Response	CR	PR	NC	PD	Other	Total
HAC alone	9	7	11	6	2	35
HAC + SIRT	16	13	2	1	7	39

CR - complete response, PR - partial response, NC - no change, PD - progressive disease
Difference between groups (Kruskal-Wallis test for categories CR, PR, NC, and PD) p=0.002

It should be noted that tumour volume was measured independently by two readers who were blinded to treatment allocation of the patients and were independent to the trial. Tumour area, however, was measured by only one reader (the primary investigator) and was not evaluated blind to treatment allocation or any other clinical data. The potential for reporting bias in such a situation should be noted.

An attempt was made by the applicant to address the issue of potential reporting bias by having the CT scans previously assessed by the primary investigator, re-analysed by a blinded and independent researcher. Table 24 indicates the results of this re-analysis on response, as measured by tumour area. The applicant has indicated that results for tumour volume remained virtually unchanged.

Table 24 Re-analysis of tumour response as measured by tumour area (all patients)

Response	CR	PR	NC	PD	Other	Total
HAC alone	1	7	11	10	6	35
HAC + SIRT	2	16	12	6	3	39

CR – complete response, PR – partial response, NC – no change, PD – progressive disease
Difference between groups (Kruskal-Wallis test) p=0.047

Systemic Chemotherapy + SIRT

The authors indicate that tumour response was measured using the RECIST criteria (Appendix F), but do not state whether assessment was based on tumour area or tumour volume. First integrated response and best confirmed response are presented in Tables 25 and 26.

Table 25 Tumour response by first integrated response

Response	CR	PR	NC	PD	Total
Chemotherapy alone	0	0	6	4	10
Chemotherapy + SIRT	0	10	1	0	11

CR – complete response; PR – partial response; NC – no change; PD – progressive disease
Difference between groups (Kruskal-Wallis) p<0.001

Table 26 Tumour response by best confirmed response

Response	CR	PR	NC	PD	Total
Chemotherapy alone	0	0	6	4	10
Chemotherapy + SIRT	0	8	3	0	11

Note: CR – complete response, PR – partial response, NC – no change, PD – progressive disease
Difference between groups (Kruskal-Wallis) p<0.001

Uncontrolled evidence

Uncontrolled evidence of the use of selective internal radiation therapy is unlikely to provide a great deal of additional information due to inconsistencies in the way efficacy data is reported between papers. The small patient numbers in many of these papers also limits the generalisability of information reported here.

Tumour response

Andrews et al (1994a) indicated that of 17 patients treated with TheraSphere® alone, 10 (58%) had some response to treatment (either partial response, minimal response or stable disease). Many papers reported tumour response as a simple measure of decrease or stability in lesion size ('size', 'area' or 'volume'). A decrease in lesion size was reported in 43% (7/16) of patients by Blanchard (1989b), 62% (18/29 and 44/71) of patients by Gray (1992f),(2000b) and 73% (32/44) of patients at three months and 82% (23/28) at six months by Stubbs (2001). Herba (1988h) found that 10/15 (67%) patients had stable disease at a mean follow-up of four months, while an additional 18% (8/44) of patients in the Stubbs paper (2001) had stable disease at three months and 14% (4/28) at six months.

Survival

Very few papers reported on survival of patients, and in many it was not possible to determine when survival was measured from (eg therapy, diagnosis etc). Andrews et al (1994a) found that the median survival of patients treated with internal radiation therapy alone was 60 weeks. Blanchard (1989b) indicated a median survival of 55 weeks for patients treated with internal radiation therapy, while Gray (2000b) demonstrated a median survival of 9.9 months from SIRT administration and 17.3 months from diagnosis of liver metastases. Stubbs et al (2001) indicated that after a median follow-up of 25.5 months, median survival from the time of diagnosis of liver metastases was 14.5 months and from time of treatment was 9.8 months.

Conclusions

- Quality adjusted survival (quality adjusted life years - QALYs) was not reported in either randomised trial. Neither trial was adequately powered to detect a difference in quality of life measures.

- There was no statistically significant difference in overall survival between patients treated with hepatic arterial chemotherapy and those treated with hepatic arterial chemotherapy plus SIRT, although the trial was insufficiently powered to detect moderate but clinically important differences in overall survival. Overall survival was not reported in the trial of systemic chemotherapy plus SIRT versus systemic chemotherapy alone.

- There was no statistically significant difference in progression-free survival between patients treated with hepatic arterial chemotherapy and those treated with hepatic arterial chemotherapy plus SIRT, although the trial was insufficiently powered to detect clinically important differences in progression-free survival.

- The trial of systemic chemotherapy plus SIRT versus systemic chemotherapy alone indicated that the time to progressive disease in the combination arm was significantly longer.

- In the outcome of time to disease progression in the liver, there was some evidence of a benefit favouring SIRT plus hepatic chemotherapy, depending upon how disease progression in the liver was measured.

  - If disease progression was measured by tumour volume (blinded), there was a trend favouring SIRT plus hepatic chemotherapy.

  - If disease progression was measured by tumour area (unblinded) and analysed using a competing risks model then there was a statistically significant difference in favour of the addition of SIRT to hepatic arterial chemotherapy ($p=0.033$, Gray's test).

- In the outcome of tumour response, there was some evidence of a benefit favouring SIRT plus hepatic chemotherapy over hepatic chemotherapy alone, depending upon how tumour response was measured.

  - If tumour response was measured by tumour volume (blinded), there was a trend favouring SIRT plus hepatic chemotherapy ($p=0.06$).

  - If disease progression was measured by tumour area (unblinded) there was a statistically significant difference in favour of the addition of SIRT to hepatic arterial chemotherapy ($p=0.02$).

  - When re-analysed in a blinded manner, there was still a statistically significant difference in favour of the addition of SIRT to hepatic arterial chemotherapy ($p=0.047$).

- In the trial of systemic chemotherapy plus SIRT versus systemic chemotherapy alone, tumour response, as measured by first integrated response and best confirmed response was significantly higher for patients treated with systemic chemotherapy plus SIRT compared to patients treated with systemic chemotherapy alone.

What are the economic considerations?

Estimated Utilisation

Colorectal cancer is the most common cancer reported to Australian cancer registries. In 1997, there were 11,245 new cases of colorectal cancer reported and 4,678 deaths, accounting for approximately 14.1% of all new cases of cancer (excluding non-melanocytic skin cancer) and 13.8% of cancer related deaths (Australian Institute of Health and Welfare & Australasian Association of Cancer Registries 2000).

It is estimated that fifty per cent of patients with colorectal cancer will develop liver metastases within five years (Clinical Oncology Society of Australia & Australian Cancer Network 1999; Taylor 1996). In 20-40% of patients, this will be the only (or first) site of failure (Clinical Oncology Society of Australia & Australian Cancer Network 1999).

It is difficult to estimate how many patients might receive treatment with surgical resection alone. It is equally as difficult to try to estimate the numbers of patients from those not eligible for surgery who would receive systemic chemotherapy and how many may be considered for hepatic chemotherapy, as treatment practices for chemotherapy vary around Australia.

The table below indicates the number of occurrences of implantation of a port for delivery of cytotoxics from July 1998 until June 1999, however, as this data is only available for New South Wales, Victoria, Australian Capital Territory and Northern Territory (as these are the only states and territories that have instituted ICD-10-AM coding), it is likely to be an underestimate of the true number of people who have received hepatic arterial chemotherapy over this time.

Table 27 Occurrences of principal procedure likely to be associated with hepatic arterial chemotherapy and SIRT

ICD- code		Procedure	Year	Table	Total number of occurrences (Public and Private)
30400-00	ICD-10*	Ins VAD w atchmt intra-abdo vesl cath	1998-99	Table 13	162

*ICD-10 only available for NSW, Victoria, ACT and Northern Territory; (Commonwealth Department of Health and Aged Care 2001)

It is unclear how many patients may receive HAC + SIRT instead of HAC alone, or indeed instead of systemic chemotherapy alone, if SIRT was approved for funding.

Incremental Costs

As discussed previously, it was decided *a priori* that the economic evaluation of SIRT would be conducted against a comparator of hepatic arterial chemotherapy. The incremental cost of adding SIRT to hepatic chemotherapy has been calculated (Table 28). Scenarios based on one and four days hospitalisation following administration of SIRT have been examined. All costs have been rounded to the nearest dollar.

Table 28 Incremental cost of HAC + SIRT over HAC alone

Procedure	Item number or Unit cost	Reference	HAC (via port)	HAC + SIRT (4 day stay after SIRT)	HAC + SIRT (1 day stay after SIRT)
Insertion of PORT					
Implantation of PORT	30400	Medicare Schedule	$492	$4920	$492
Cholecystectomy*	30443	Medicare Schedule	$576	$576	$576
Anaesthesia fee*	17713	Medicare Schedule	$192	$192	$192
Hepatic angiogram	60078	Medicare Schedule	$136	$136	$136
	60027	Medicare Schedule	$780	$780	$780
	59921	Medicare Schedule	$104	$104	$104
Theatre fee		Application	$1,800	$1,800	$1,800
Hospital stay after port insertion (days)		Application	4	4	4
Cost per Hospital day	$420	Application			
Cost of hospital stay after port insertion			$1,680	$1,680	$1,680
SIRT Delivery					
Technetium scan for lung-liver breakthrough	61499	Medicare Schedule	n/a	$221	$221
SIRT handling and administration	15331	Medicare Schedule	n/a	$581	$581
Cost of SIRT		Application		$6,800	$6,800
Hospital stay after SIRT administration (days)			n/a	4*	1**
Cost per Hospital day	$420	As above			
Cost of hospital stay after SIRT administration			n/a	$1,680	$420
Angiotensin II inhibitor		PBS	n/a	$1	$1
H-2 inhibitor		PBS	n/a	$10	$10
Anti-nausea medication		PBS	n/a	$5	$5
Chemotherapy delivery			Equivalent	Equivalent	Equivalent
Total costs (excluding chemotherapy)[1]			$5,760	$15,058	$13,798
Incremental Cost of SIRT over HAC alone				$9,298	$8,038

* NHMRC Guidelines; ** Applicant

[1] assumed an equivalent duration and type of chemotherapy for HAC alone and HAC + SIRT patients

As discussed earlier, the duration of stay in hospital after administration of SIRT has been costed at one day by the applicant. However, the current NHMRC recommendation (National Health and Medical Research Council 1984) on discharge of patients who have undergone treatment with radioactive substances specifies that discharge should not occur until total activity remaining in the patient has dropped to 1200 MBq. As the dose of yttrium-90 delivered for SIRT is 2-4 GBq, and the half life is >67 hours, the patient may require a 3-4 day hospital stay.

The incremental cost of administering SIRT plus HAC over HAC alone ranges between $8,038 and $9,298, depending upon the length of hospital stay after SIRT administration.

Incremental Effectiveness

As the differences between overall survival and progression-free survival in the randomised trial of HAC plus SIRT versus HAC alone were not statistically significant, it is not appropriate to calculate incremental cost effectiveness ratios based on final outcomes. A clinical endpoint, such as tumour response (as measured by response in the liver) is the only measure available from this trial upon which cost effectiveness can be calculated.

The applicant classified tumour response as the aggregation of patients who had a complete response (CR), partial response (PR) or no change (NC). The conventional measure of tumour response, however, only includes patients with a complete response (CR) or partial response (PR) to therapy. Data in Table 29 are from both the original analysis, where the primary investigator assessed tumour response and the re-analysis where a blinded independent reader conducted the assessment of tumour response. Tumour response is classified as CR + PR, calculations are presented in Appendix E.

Table 29 Response rates as measured by tumour area (all patients) (CR + PR)

Variable	Original analysis		Re-analysis	
Treatment group	SIRT + HAC	HAC alone	SIRT +HAC	HAC alone
Total number	39	35	39	35
Number with CR	2	0	2	1
Number with PR	14	6	16	7
Total number with response	16	6	18	8
Response rate	41% (16/39)	17% (6/35)	46% (18/39)	23% (8/35)
Difference in response rate	24%		23%	
95% Confidence interval around difference	4% to 45%		1% to 43%	
p value (Fisher's exact test)	0.04		0.05	

CR –complete response; PR – partial response

Incremental cost effectiveness ratio (ICER)

The incremental cost effectiveness ratio of HAC + SIRT over HAC alone is calculated as follows:

$$\text{ICER} = \frac{\text{Total Cost of HAC + SIRT} - \text{Total cost of HAC alone}}{\text{Proportion of responders to HAC + SIRT} - \text{Proportion of responders to HAC alone}}$$

Tables 30 and 31 provide the incremental cost effectiveness ratio for SIRT plus HAC over SIRT for both the original tumour response data and the re-analysed tumour response data. Costs remain constant for both analyses.

Table 30 Incremental costs and benefits of SIRT (original data)

	HAC alone	HAC + SIRT (4 day hospital stay)	Incremental difference	HAC + SIRT (1 day hospital stay)	Incremental difference
	(1)	**(2)**	**(2) – (1)**	**(3)**	**(3) – (1)**
Total cost	$5,760	$15,058	**$9,298**	$13,798	**$8,038**
Total benefit (proportion of patients with any response (in the liver) to treatment)	0.17	0.41	0.24	0.41	0.24
ICER		**$38,742 per additional patient with a response in the liver**		**$33,492 per additional patient with a response in the liver**	
95% CI around difference in proportion of responders		0.04 to 0.45		0.04 to 0.45	
95% CI around ICER		**$20,662 to $232,450**		**$17,862 to $200,950**	

Calculations are not exact, as data has been rounded

Table 31 Incremental costs and benefits of SIRT (re-analysed data)

	HAC alone	HAC + SIRT (4 day hospital stay)	Incremental difference	HAC + SIRT (1 day hospital stay)	Incremental difference
	(1)	**(2)**	**(2) – (1)**	**(3)**	**(3) – (1)**
Total cost	$5,760	$15,058	**$9,298**	$13,798	**$8,038**
Total benefit (proportion of patients with any response (in the liver) to treatment)	0.23	0.46	0.23	0.46	0.23
ICER		**$39,911 per additional patient with a response in the liver**		**$34,503 per additional patient with a response in the liver**	
95% CI around difference in proportion of responders		0.01 to 0.43		0.01 to 0.43	
95% CI around ICER		**$21,626 to $669,017**		**$18,696 to $578,356**	

Calculations are not exact, as data has been rounded

Conclusions

- Treatment practices for hepatic metastases vary between hospitals in Australia
- True estimates of the number of patients who might use this therapy if it were available are difficult to obtain. The reasons for this are:
  - It is unclear how many patients currently receive treatment with hepatic chemotherapy, and how many of these patients would also receive SIRT if it was approved; and
  - It is unclear how many patients who are currently treated with systemic chemotherapy would be changed to treatment with HAC plus SIRT if it was available.
- Costs included here are direct medical costs and do not take into account indirect or societal costs.

- Using data from the original analysis, the incremental cost-effectiveness ratio for SIRT is $38,742 per additional patient who has a response in the liver. Depending upon assumptions outlined above and the 95% confidence interval of the estimate of benefit, this might plausibly be as low as $17,862 or as high as $232,450 per additional patient who has a response in the liver

- Using data from the re-analysis, the incremental cost-effectiveness ratio for SIRT is $39,911 per additional patient who has a response in the liver. Depending upon assumptions outlined above and the 95% confidence interval of the estimate of benefit, this might plausibly be as low as $18,696 or as high as $669,017 per additional patient who has a response in the liver.

Conclusions

Safety

Patient safety

The randomised trials provided limited information regarding patient safety. It appears that the addition of SIRT to hepatic arterial chemotherapy may result in additional elevation of hepatic enzymes (alkaline phosphatase), and more nausea and vomiting than hepatic arterial chemotherapy alone. Similarly, the addition of SIRT to systemic chemotherapy appeared to result in more grade 3-4 toxicities (including granulocytopenia and mucositis) than did systemic chemotherapy alone. There was one treatment related death in the combined treatment arm of this trial.

In both trials, patients often experienced abdominal pain after administration of SIR-Spheres which in some cases required narcotic analgesia.

Uncontrolled evidence suggests that administration of selective internal radiation therapy (with SIR-Spheres, or other similar agents) will commonly result in liver enzyme elevations, fatigue and lethargy, anorexia, nausea and/or vomiting and gastrointestinal symptoms. There have been a small number of cases of fatal radiation hepatitis, gastrointestinal ulceration or haemorrhage, and radiation pneumonitis.

Personnel safety

From data reported in a small number of publications, and from information supplied by the applicant, it would appear that the doses of radiation delivered to personnel are reasonably low and are within ranges recommended by the National Occupational Health and Safety Commission (National Occupational Health and Safety Commission 1995). The current NHMRC recommendation (National Health and Medical Research Council 1984) on discharge of patients who have undergone treatment with radioactive substances specifies that discharge should not occur until total activity remaining in the patient has dropped to 1200 MBq. As the dose of yttrium-90 delivered for SIRT is 2-4 GBq, and the half life is >67 hours, the patient may require a 3-4 day hospital stay (not the one day stay as in the randomised controlled trial) before reaching this level.

Effectiveness

There is some evidence that addition of SIRT to hepatic chemotherapy may be more effective than hepatic chemotherapy alone in terms of tumour response in the liver. Depending upon the method of measuring tumour response, there may have been improved tumour response rates for patients receiving treatment with SIRT. When tumour response was measured by changes in tumour volume, there was a trend favouring SIRT plus hepatic chemotherapy in tumour response. When tumour response was measured by tumour area, patients treated with hepatic chemotherapy plus SIRT had significantly more tumour responses than patients treated with chemotherapy alone.

There is also some evidence to suggest that the addition of SIRT to systemic chemotherapy offered improvements in tumour response as measured by both 'first integrated response' and 'best confirmed response'

The addition of SIRT to hepatic chemotherapy may prolong time to disease progression in the liver. Depending upon the method of measuring disease progression in the liver, there may have been a benefit for patients receiving SIRT in addition to hepatic chemotherapy. If disease progression was measured by tumour volume, there was a trend favouring SIRT plus hepatic chemotherapy in time to first disease progression in the liver. If disease progression was measured by tumour area, and analysed with a competing risks model, there was a significant difference favouring SIRT plus hepatic chemotherapy ($p=0.033$, Gray's test).

There is insufficient evidence from the trial of hepatic chemotherapy plus SIRT to determine the effect of SIRT on progression-free or overall survival. There was no statistically significant difference in overall or progression-free survival between patients treated with hepatic arterial chemotherapy and those treated with hepatic chemotherapy and SIRT. However, the trial was insufficiently powered to detect a moderate and clinically important difference in overall and progression-free survival.

The small trial of systemic chemotherapy plus SIRT versus systemic chemotherapy alone suggested that the time to progressive disease in the combination arm was significantly longer, however, overall survival was not measured.

Quality adjusted survival was not reported in either randomised trial. Neither trial was adequately powered to detect a difference in quality of life measures.

Cost-effectiveness

It is not possible to give a reliable estimate of cost per life year saved (LYS) or cost per quality adjusted life year (QALY) due to the lack of reliable evidence of benefit on these outcomes.

Using data from the original analysis, the incremental cost-effectiveness ratio for SIRT is $38,742 per additional patient who has a response in the liver. Depending upon assumptions and the 95% confidence interval of the estimate of benefit, this might plausibly be as low as $17,862 or as high as $232,450 per additional patient who has a response in the liver.

Using data from the blinded re-analysis of tumour response, the incremental cost-effectiveness ratio for SIRT is $39,911 per additional patient who has a response in the liver. Depending upon assumptions and the 95% confidence interval of the estimate of benefit, this might plausibly be as low as $18,696 or as high as $669,017 per additional patient who has a response in the liver.

A comprehensive Australian-based assessment of costs and effects associated with systemic chemotherapy, hepatic arterial chemotherapy and SIRT is needed to provide a basis for a comparison between systemic therapy and hepatic chemotherapy with or without SIRT.

Recommendation

Since there is currently insufficient evidence of effectiveness and cost-effectiveness for Selective Internal Radiation Therapy (SIRT) using SIR-spheres®, MSAC recommended that public funding should not be supported at this time for this procedure.

The data suggests that the treatment is reasonably safe and has anti-tumour activity. However, it is not clear whether this anti-tumour activity translates into a survival or quality of life benefit to the patient.

- The Minister for Health and Ageing accepted this recommendation on 28 August 2002 -

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC), and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise or Affiliation**
Mr Stephen Blamey (Chair)	general surgery
Professor Bruce Barraclough	general surgery
Professor Syd Bell	pathology
Dr Paul Craft	clinical epidemiology and oncology
Professor Ian Fraser	reproductive medicine
Associate Professor Jane Hall	health economics
Dr Terri Jackson	health economics
Ms Rebecca James	consumer health issues
Professor Brendon Kearney	health administration and planning
Mr Alan Keith	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Ageing
Associate Professor Richard King	internal medicine
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Mr Lou McCallum	consumer health issues
Emeritus Professor Peter Phelan	paediatrics

Dr Ewa Piejko	general practice
Dr David Robinson	plastic surgery
Professor John Simes	clinical epidemiology and clinical trials
Professor Richard Smallwood	Chief Medical Officer, Commonwealth Department of Health and Ageing
Professor Bryant Stokes	neurological surgery, representing the Australian Health Ministers' Advisory Council
Associate Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Professor David Weedon	pathology (Chair until 24/08/01)
Ms Hilda Bastian	consumer health issues (Member until 24/08/01)
Dr Ross Blair	vascular surgery (New Zealand) (Member until 24/08/01)
Dr Paul Hemming	general practice (Member until 24/08/01)

Appendix B Supporting committee

Supporting committee for MSAC application 1034 Selective Internal Radiation Therapy using SIR-Spheres

Dr John Primrose (Chair) MB BS (Hons), FRACR Senior Medical Adviser, Health Access and Financing Division Commonwealth Dept of Health and Ageing	Medical Adviser to MSAC
Mr Stephen Blamey BSc, MBBS, FRACS Consultant General and Gastrointestinal Surgeon Monash Medical Centre, Melbourne	Chair of MSAC
Dr David Macfarlane MBBS Hons, FRACP Staff Specialist, Department of Nuclear Medicine, Royal Brisbane Hospital	Nominated by the Australian and New Zealand Association of Physicians in Nuclear Medicine (ANZAPNM)
Mr Russell McGowan Consumer Representative Health Care Consumers' Association of the ACT	Nominated by the Consumer Health Forum
Professor John Zalcberg MBBS, PhD, FRACP Director, Haematology and Medical Oncology Peter MacCallum Cancer Institute, Melbourne	Nominated by the Medical Oncology Group of Australia

Appendix C Included studies

Controlled evidence

Quality assessment of submitted publications of randomised controlled trials (Gray et al. 2000a; Gray et al. 2001d) and in-confidence data from the manufacturer's application for the trial of HAC plus SIRT versus HAC alone (SIRTeX Medical Ltd. 2000c) was conducted using the MERGE instrument, Checklist 2 – Studies assessing the effect of interventions (Liddle, Williamson, & Irwig 1996).

Evaluation criteria for the study containing the main components of study quality to be considered are shown in Table 32. The evaluation of the quality of a study, review or guideline provides information to assist in deciding whether researchers or guideline developers have taken the necessary steps to prevent the over- or underestimation of the true effect of interventions, risk factors, diagnostic test accuracy and guideline recommendations.

Table 32 Coding for evaluation criteria

Evaluation criteria are coded according to the extent to which the criteria are fulfilled	Code
Criterion entirely fulfilled	a
Criterion mostly fulfilled	b1
Criterion mostly not fulfilled	b2
Criterion not at all fulfilled	c
Criterion not described adequately to classify as (a), (b1), (b2) or (c)	?
Criterion not applicable	n/a

Overall assessment of the study allows the reviewer to assess and code the overall quality of the study using the codes in Table 33. Study quality is coded as A, B1, B2, C - these codes are intended to be compatible with those of the Cochrane Collaboration.

Table 33 Codes for overall assessment of quality of study checklists

Level of Bias	Code	Explanation
Low risk of bias	A	Al l or most evaluation criteria from the checklist are fulfilled. Where evaluation criteria are not fulfilled, the conclusions of the study or review are thought very unlikely to alter.
Low – moderate risk of bias	B1	Some evaluation criteria from the checklist are fulfilled. Where evaluation criteria are not fulfilled or are not adequately described, t he conclusions of the study or review are thought unlikely to alter.
Moderate – high risk of bias	B2	Some evaluation criteria from the checklist are fulfilled. Where evaluation criteria are not fulfilled or are not adequately described, t he conclusions of the study or review are thought likely to alter.
High risk of bias	C	Few or no evaluation criteria fulfilled. Where evaluation criteria are not fulfilled or are not adequately described, the conclusions of the study or review are thought very likely to alter.

Table 34 Assessment of SIRT trials

Descriptive information abut the study	Notes	Description	
		HAC + SIRT vs HAC alone	**Systemic chemo + SIRT vs Systemic chemo alone**
Study identification	*Include author, title, reference and year of publication (if available) and the study timeframe*	This checklist assesses both the trial report and the submitted publication from Gray et al, of HAC versus HAC + SIRT	Unpublished trial data (publication submitted) study timeframe not stated
How is the study described?	*Randomised controlled trial (RCT), non-randomised controlled trials (N-RCS), cohorts, before and after studies (BAS) with/without controls, case control studies (C-CS) – define whether population or hospital-based case control study*	RCT	RCT
What interventions are considered and how are they implemented?		Hepatic arterial chemotherapy compared to hepatic arterial chemotherapy plus selective internal radiation therapy using SIR-Spheres	Systemic chemotherapy compared to systemic chemotherapy plus selective internal radiation therapy using SIR-Spheres
Is the intervention aimed at individuals or populations?	*eg drug trial (for individuals), mass media campaign (for populations)*	Individuals	Individuals
What outcomes are considered?	*ie benefits and harms*	Tumour response to therapy (measured by tumour area, tumour volume and CEA); time to progressive disease (at any site, liver) survival, QOL, toxicity	Tumour response to therapy measured by RECIST criteria: first integrated response, best confirmed response; time to progressive disease, QOL, toxicity
What factors other than the intervention could affect the outcomes	*Include potential confounding factors, differences in baseline characteristics between intervention and control groups*	Baseline characteristics: age, sex, regional lymph node involvement, size of liver metastases; prior treatment for liver metastases, time from diagnosis of liver metastases to randomisation Administration of non-protocol chemotherapy	Baseline characteristics: age, sex, regional lymph node involvement, size of liver metastases; prior treatment for liver metastases, time from diagnosis of liver metastases to randomisation Administration of non-protocol chemotherapy
What are the characteristics of the population and study setting?	*Population characteristics eg age, sex, disease characteristics of the population, disease prevalence. Study setting eg rural, urban, hospital inpatient or outpatient, general practice, community*	74 patients (70 'eligible patients') between May 1, 1991 and May 1, 1997; trial design specified recruitment of 95 patients, but trial was stopped early; 57M, 17F age range not indicated Two teaching hospitals in Perth	21 patients (10 control, 10 experimental) unstated recruitment period Three Australian hospitals (2 WA, 1 Qld)
How many groups / sites in the study?		Two	Three

Evaluation Criteria for the study					Comments		Code Options a, b1, b2, c, ?, n/a	
					HAC + SIRT	**Systemic chemotherapy + SIRT**	**HAC + SIRT**	**Syst. Chemo + SIRT**
What is the Study Type?					RCT	RCT		
RCT	*N-RCS*	*Cohort*	*BAS*	*C-CS*				
Are the study participants well-defined in terms of time, place and person?							n/a	n/a
	N-RCS	*Cohort*	*BAS*	*C-CS*				
Is the method of allocation to intervention and control groups/sites independent of the decision to enter the individual or group in the study (adequate allocation concealment)?					It is unclear from the trial report or the submitted publication what the method of randomisation was. The protocol indicates that randomisation was achieved by a blind code envelope in a blocked randomisation format	Randomisation achieved by calling an off-site independent randomisation centre	b1	a
RCT								
What percentage (%) of individuals or clusters refused to participate?							n/a	n/a
	N-RCS	*Cohort*	*BAS*	*C-CS*				

Evaluation Criteria for the study					Comments		Code Options a, b1, b2, c, ?, n/a	
Are individuals within groups/clusters blind to which intervention group they belong AND are those delivering the intervention (health professionals, carers) blind to the intervention group?					No- patients and staff were not blinded to treatment allocation	No- patients and staff were not blinded to treatment allocation	c	c
RCT	*N-RCS*							
Is exposure to interventions measured in a standard, valid and reliable way (avoidance of recall bias)?							n/a	n/a
				C-CS				
Is exposure to interventions measured in the same way for both case and control groups? (NB objective measures would meet this criteria)							n/a	n/a
				C-CS				
Are outcomes measured in a standard, valid and reliable way?					Tumour Area, the conventional response measure was measured by 1 doctor (the primary investigator) who was not blinded to treatment allocation - possibility of bias introduced into area measurement Tumour volumes were measured by 2 independent doctors who were blinded to treatment allocation	Tumour response based on RECIST criteria (unclear whether these are conventional criteria in Australia) CT scans read by blinded independent experienced reader	b2	b1
RCT	*N-RCS*	*Cohort*	*BAS*	*C-CS*				
Are outcomes measured in the same way for both intervention and control groups? (NB Blinding or objective measures would meet this criteria)					Appears to be the same for both groups but tumour areas were measured by 1 doctor involved in the selection and treatment of patients who was not blind to treatment allocation	Blinded interpretation of CT scans for tumour response	b1	a
RCT	*N-RCS*	*Cohort*	*BAS*	*C-CS*				
Are factors other than the intervention eg confounding factors, comparable between intervention and control groups and if not comparable, are they adjusted for in the analysis?					Appear to be comparable between groups	Appear to be comparable between groups	a	a
RCT	*N-RCS*	*Cohort*	*BAS*	*C-CS*				
What percentage (%) of individuals or clusters recruited into the study are not included in the analysis? (loss to follow up)					In the trial report, many outcomes were reported in 2 ways: eligible patients only and all patients, for some outcomes eg survival, it is not possible to tell whether all or eligible only patients were used The submitted paper includes only eligible patients Original trial designed to recruit 95 patients, trial stopped at 74	Appears all patients randomised have been included in analysis	b1	a
RCT	*N-RCS*	*Cohort*	*BAS*	*C-CS*				
Is the analysis by intention to intervene (treat)?					In the trial report, many outcomes were reported in 2 ways: eligible patients only and all patients, for some outcomes eg survival, it is not possible to tell whether all or eligible only patients were used The submitted paper includes only eligible patients		b1 (trial report) c (submitted paper)	a
RCT	*N-RCS*		*BAS*					
Are results homogenous between sites? (multicentre / multisite studies only)					Results are not reported separately for individual centre, criteria cannot be assessed	Results are not reported separately for individual centre, criteria cannot be assessed	?	?
RCT	*N-RCS*	*Cohort*	*BAS*	*C-CS*				

Overall assessment of the study	**Comments**		**Code options A, B1, B2, C**	
How well (code A, B1, B2, C – see Table 33) was the study done to minimise bias? If coded to B1, B2, or C, what is the likely direction in which bias might affect the study results?	Patients and investigators not blinded; there was not concealment of treatment allocation; the submitted paper only reports data on eligible patients, is not an ITT; trial report: for some endpoints, it cannot be determined whether ITT or eligible only analysis ; the most conventional measure of tumour response to treatment (tumour area) was measured by only 1 author (the primary investigator) who was likely not blinded; while this is probably not going to affect the overall direction of the outcome, it may lead to an overestimation of the true effect of SIR-Spheres on tumour response and therefore of true therapeutic benefit.	Patients and investigators not blinded to treatment allocation, but assessment of CT scan (tumour response outcome) is assessed by blinded independent reader randomisation performed offsite by independent group	B1 some criteria fulfilled, where not fulfilled, or described, conclusions thought unlikely to alter	A All or most criteria fulfilled; where not fulfilled, conclusions unlikely to alter.
Is the overall effect of the study due to the study intervention?	Probably	Likely		
If the study type is not an RCT, explain if there is any practical or ethical reason why an RCT cannot be done.	n/a	n/a		
Include other comments concerning areas for further research, applicability of evidence to target population, importance of study to policy development	n/a	Small study size is the major limitation of this trial (n=21)		

The following page (Page 50) has been left blank intentionally.

Table 35 Patient data and results from uncontrolled evidence

Study	LM or PLC*	N*	Type of microspheres	Institution	Study perspective	Patient characteristics	Efficacy data (if applicable*, **	Safety Data	Comments*
(Andrews et al. 1994a)	LM + PLC	24 n=17 LM from CRC n=6 LM from neuroendocrine tumours n=1 PLC	Glass matrix TheraSphere®	University of Michigan Medical Centre, Ann Arbor	Prospective Phase I study, clearly defined inclusion criteria Dose ranging study to determine hepatic tolerance	Failed conventional therapy, no prior radiotherapy; CT evidence of PD Estimated whole liver dose 5000cGy (2pts); 7500cGy (6pts); 10000cGy (7pts); 12500cGy (6pts); 15000cGy (3 pts)	17 LM from CRC PR (5); minimal response (1); SD (4); PD (7) Median survival 60 weeks Neuroendocrine LM (6) Minimal response (3); SD (3) PLC: (1) PD	Mild transient increases in transaminase levels (all); transient fever (4); fatigue (18); gastritis (4) No pulmonary fibrosis noted with 53 months followup No hepatic or haematological toxicity	Not used in combination with any HAC
(Blanchard, Morrow, & Sutherland 1989b)	LM + PLC	16 treated n=8 LM from CRC, n=3 LM from carcinoid; n=4 LM from other tumours; n=1 PLC 20 controls	Carbonised plastic	University of Manitoba, Health Sciences Centre, Winnipeg, Manitoba, Canada	Prospective: 09/76 to 09/78 40 patients screened clinically, 36 with angiography 16 had active treatment; 20 patients not eligible acted as 'control group'	Treated patients: 7F, 9M No other information	13/16 had follow up angiography n=5 tumour decreased to < 50% of pre=trtmt diameter and to < 13% of pre-trtmt volume; n=2 decrease of at least 50% in tumour volume Survival: treated Mean = 62 wks; Mdn = 55wks Survival control Mean = 30wks; Mdn = 22 wks	Transient hepatic enzyme elevation, n=3/16 Radiation gastritis n=2 Ulcer n=2; ulcer requiring surgery, n=1; radiation gastritis and ulcer n=1 Nausea n=5 Anorexia n=5 No cholecystitis or pancreatitis	Predetermined criterion of effective treatment: 50% decrease in calculated volume of hepatic tumour on follow-up
(Grady et al. 1983c)	LM + PLC	16 n=13 LM from CRC n=1 LM from adrenal tumour n=1 LM from breast n=1 PLC	Resin	Georgia Institute of Technology and Emory University Clinic, Atlanta, US	? perspective; assume all patients treated over previous 3 years	n/a	No response data reported	Fatal radiation hepatitis, n=1 Peptic ulceration, n=1	Combined with regional hyperthermia
(Gray et al. 1992f)	LM from CRC	29	SIR-Spheres	Royal Perth Hospital, Perth, Western Australia, Australia	?unclear whether selected patients or consecutive patients No date ranges reported Assume retrospective	N=24 no prior therapy for LM n=4 previous HAC only; N=1 HAC and systemic trtmt	Efficacy measured by tumour volume and CEA, no tumour area data Tumour volume (22/29 eval) N=18 had a decrease in tum. Vol. (10 > 50% decrease) N=4 had an increase in tum. Vol. CEA (26/29 eval) N=23 >50% decrease in CEA N=9 CEA normalised	No safety data reported	Unclear whether patients are selected or consecutive It is unclear how many patients were not evaluated (report says 7, 8 and 9 in different places) It is unclear at what time point efficacy was evaluated

* LM – Liver metastases; PLC - primary liver cancer; CRC – colorectal cancer; FUDR – floxuridine; CT - computed tomography; US - ultrasound

**Response criteria: CR – complete response; PR: partial response; SD: stable disease; PD: progressive disease; PT: pre-treatment

Table 35 Patient data and results from uncontrolled evidence (continued)

Study	LM or PLC*	N*	Type of microspheres	Institution	Study perspective	Patient characteristics	Efficacy data (if applicable*, **	Safety Data	Comments*
(Gray et al. 2000b)	LM from CRC	71 (62 'evaluable') 66 had 1 x SIRT 5 had 2 x SIRT	SIR-Spheres	Royal Perth Hospital, Perth, Western Australia, Australia	Consecutive patients No date range provided Unclear whether prospective or retrospective	43M, 28F 33-76 yrs	Efficacy measured by tumour volume and CEA, no tumour area data Tumour volume (51/71 eval) N=7 volume increase N=6 <30% volume decrease N=38 >30% volume decrease (28 had > 50% volume decrease) (PR) CEA (60/71 evaluable) N=3 CEA increased N=4 CEA decrease <50% on PT levels (=SD) N=22 CEA decr. to normal (CR) N=31 CEA decrease ≥ 50%, but not normalised (PR) Survival Mdn survival from SIRT administration: 9.9 mo Mdn survival from diagnosis of liver metastases: 17.3 mo	N=1 fatal radiation hepatitis No cases of biliary sclerosis Transient abdominal pain and nausea common	Authors report that there 'was the intention to treat all patients with ≥1 cycle FUDR for 12 days per cycle, repeated until disease progression to be started within 24 hours of SIRT" N=33 had additional chemotherapy after FUDR CEA PR = >50% ? in CEA CR = ? in CEA to normal Tumour volume PR = >30% ? in volume (> 50% also measured)
(Herba et al. 1988h)	LM + PLC	15 n=12 LM from CRC n=1 LM from carcinoid n=1 LM from islet cell n=1 PLC	Glass TheraSphere	Montreal General Hospital, Montreal, Quebec, Canada	Prospective Phase I/II study Clear protocol defined inclusion criteria To assess toxicity and any preliminary therapeutic response	12M, 3 F mean age 62 (50-74 yrs) Three dose levels 5000 cGy (10 pts) 7500 cGy (3 pts) 10000 cGy (2 pts)	Mean follow up 7 months (2-12) N=10 had SD (@ mean f/up of 4mo [2-12]) N=5 had PD (@ mean f/up 7.5 mo [7-8]) N=2 had a decrease in tumour marker	14/15 incr. liver enzymes 1/15 WBC fluctuations (few weeks), no other haem FX 2/15 mild, temporary incr. serum bilirubin 3/15 pyloric ulceration / duodenitis 6-8 weeks after treatment 1/15 GI tract haemorrhage with history (2-3 yrs previously) bleeding duodenal ulcer	7 followed up with CT; 7 followed up with US, 2 were followed by both one patient no follow up (died at 8 months with PD)
(Ho et al. 1997i)	PLC + LM	100 n=94 PLC n=6 LM	SIR-Spheres	Prince of Wales Hospital Shatin, Hong Kong	No date range reported Unclear whether consecutive or selected patients Unclear whether retrospective or prospective	Not reported	Not relevant LM efficacy data is not able to be separated from PLC data	N=1 radiation pneumonitis N=1 radiation pneumonitis after 2nd dose N=3 (with > 20% lung shunting) developed radiation pneumonitis	21 patients had multiple treatments

* LM – Liver metastases; PLC - primary liver cancer; CRC – colorectal cancer; FUDR – floxuridine; CT - computed tomography; US - ultrasound

**Response criteria: CR – complete response; PR: partial response; SD: stable disease; PD: progressive disease; PT: pre-treatment

Table 35 Patient data and results from uncontrolled evidence (continued)

Study	LM or PLC*	N*	Type of microspheres	Institution	Study perspective	Patient characteristics	Efficacy data (if applicable*, **	Safety Data	Comments*
(Lau et al. 1998j)	PLC	71	SIR-Spheres	Prince of Wales Hospital Shatin, Hong Kong	October 1992 – December 1995 Unclear whether retrospective or prospective	This is the same group of patients in Group II in (Ho et al. 1997i) above No further details reported	Not applicable	N=12 had abdominal distension, discomfort and nausea and vomiting N=10 low grade fever (transient)`	Group II of (Ho et al. 1997i) above – included as more detail on safety than in other publication
(Stubbs, Cannan, & Mitchell 2001)	LM	50 n=27 LM only n=4 also had lung metastases n=43 also received HAC with 5FU	SIR-Spheres	Wakefield Hospital, Wellington, New Zealand	Feb 1997 – June 1999 Patients selected from all patients with LM based on presence of liver disease only and fitness for laparotomy	31M, 19F Mdn age 61.4 (33-76) n=30 had <25% liver involvement (Dose: 2GBq) n13 had 25-50% liver involvement (Dose: 2.5GBq) n=7 had >50% liver involvement (Dose 3GBq)	Efficacy measured by CEA and CT for index lesion only (unclear whether tumour volume, tumour area or one dimension only) CT @ 3Mo (44/50) N=4 increase lesion size N=8 no change (SD) N=32 decrease lesion size CT @ 6Mo (28/50) N=1 increase lesion size N=4 no change (SD) N=23 decrease lesion size Median f/up 25.5 mo (8.6 – 37.5) Median survival from diagnosis of LM 14.5 mo (1.9 – 91.4) Median survival from SIRT 9.8 mo (1.0 – 30.3) KM-survival ± SE (n alive & under observation at time) 70 ± 2.3% @ 6mo (36) 45.1 ± 3.0% @ 12mo (21) 36 ± 3.0% @ 18mo (12) 14.7 ± 3.3% @ 24mo (5) 9.8 ± 3.5% @ 30mo (1)	N=14 (28%) acute pain and nausea requiring trtmt with narcotic & antiemetics N=6 duodenal ulcer within 2 mo of treatment (? Misperfusion) N=2 had a GI bleed (1 requiring surgery) All had lethargy and anorexia for 5-6 weeks	

* LM – Liver metastases; PLC - primary liver cancer; CRC – colorectal cancer; FUDR – floxuridine; CT - computed tomography; US - ultrasound

**Response criteria: CR – complete response; PR: partial response; SD: stable disease; PD: progressive disease; PT: pre-treatment

Appendix D Excluded studies

Anderson, J.H., Goldberg, J.A., Bessent, R.G., Kerr, D.J., McKillop, J.H., Stewart, I., Cooke, T.G. and McArdle, C.S. (1992) Glass yttrium-90 microspheres for patients with colorectal liver metastases. *Radiotherapy & Oncology* **25**, 137-139. [less than 10 patients]

Anonymous (1991) Two new techniques to treat inoperable liver tumors. *Oncology (Huntington)* **5**, 41 [editorial]

Ariel, I.M. and Padula, G. (1978) Treatment of symptomatic metastatic cancer to the liver from primary colon and rectal cancer by the intraarterial administration of chemotherapy and radioactive isotopes. *Journal of Surgical Oncology* **10**, 327-336. [insufficient clinical information]

Ariel, I.M. and Padula, G. (1982) Treatment of asymptomatic metastatic cancer to the liver from primary colon and rectal cancer by the intraarterial administration of chemotherapy and radioactive isotopes. *Journal of Surgical Oncology* **20**, 151-156. [insufficient clinical information]

Burton, M.A., Gray, B.N., Jones, C. and Coletti, A. (1989) Intraoperative dosimetry of 90Y in liver tissue. *International Journal of Radiation Applications & Instrumentation - Part B, Nuclear Medicine & Biology* **16**, 495-498. [dosimetry paper, no clinical data]

Burton, M.A., Gray, B.N., Klemp, P.F., Kelleher, D.K. and Hardy, N. (1989) Selective internal radiation therapy: distribution of radiation in the liver. *European Journal of Cancer & Clinical Oncology* **25**, 1487-1491. [dosimetry paper, no clinical data]

Burton, M.A., Gray, B.N., Kelleher, D.K. and Klemp, P.F. (1990) Selective internal radiation therapy: validation of intraoperative dosimetry. *Radiology* **175**, 253-255. [dosimetry paper, no clinical data]

Campbell, A.M., Bailey, I.H. and Burton, M.A. (2000) Analysis of the distribution of intra-arterial microspheres in human liver following hepatic yttrium-90 microsphere therapy. *Physics in Medicine & Biology* **45**, 1023-1033. [no clinical data]

Cao, X., He, N., Sun, J., Tan, J., Zhang, C., Yang, J., Lu, T. and Li, J. (1999) Hepatic radioembolization with Yttrium-90 glass microspheres for treatment of primary liver cancer. *Chinese Medical Journal (English Edition)* **112**, 430-432. [not liver metastases, not SIR-Spheres]

Conzone, S.D., Hafeli, U.O., Day, D.E. and Ehrhardt, G.J. (1998) Preparation and properties of radioactive rhenium glass microspheres intended for in vivo radioembolization therapy. *Journal of Biomedical Materials Research* **42**, 617-625. [technical paper, no clinical data]

Dancey, J.E., Shepherd, F.A., Paul, K., Sniderman, K.W., Houle, S., Gabrys, J., Hendler, A.L. and Goin, J.E. (2000) Treatment of nonresectable hepatocellular carcinoma with intrahepatic 90Y-microspheres. *Journal of Nuclear Medicine* **41**, 1673-1681. [not liver metastases, not SIR-Spheres]

Dong, B.W., Liang, P. and Jing, X.H. (1901) [Combined treatment of hepatic carcinoma: percutaneous intratumoral injection of Y-90 glass treatment microspheres with sonographic guidance]. [Chinese]. *Chung-Hua i Hsueh Tsa Chih [Chinese Medical Journal]* **74**, 471-473. [non-English language]

Ehrhardt, G.J. and Day, D.E. (1987) Therapeutic use of 90Y microspheres. *International Journal of Radiation Applications & Instrumentation - Part B, Nuclear Medicine & Biology* **14**, 233-242. [technical review]

Ensminger, W. (1989) Hepatic arterial chemotherapy for primary and metastatic liver cancers. *Cancer Chemotherapy & Pharmacology* **23 Suppl**, S68-S73 [review]

Erbe, E.M. and Day, D.E. (1993) Chemical durability of Y2O3-Al2O3-SiO2 glasses for the in vivo delivery of beta radiation. *Journal of Biomedical Materials Research* **27**, 1301-1308. [technical paper, no clinical data]

Feinendegen, L.E. (1994) Microdosimetric considerations of hepatic radioembolization. *Journal of Nuclear Medicine* **35**, 1644-1646. [editorial]

Fox, R.A., Klemp, P.F., Egan, G., Mina, L.L., Burton, M.A. and Gray, B.N. (1991) Dose distribution following selective internal radiation therapy. *International Journal of Radiation Oncology, Biology, Physics* **21**, 463-467. [technical paper, no clinical data]

Grady, E.D. (1979) Internal radiation therapy of hepatic cancer. *Diseases of the Colon & Rectum* **22**, 371-375. [primarily review paper, insufficient clinical data]

Grady, E.D., Auda, S.P. and Cheek, W.V. (1981) Vasoconstrictors to improve localization of radioactive microspheres in the treatment of liver cancer. *Journal of the Medical Association of Georgia* **70**, 791-795. [review]

Gray, B.N., Burton, M.A., Kelleher, D.K., Anderson, J. and Klemp, P. (1989) Selective internal radiation (SIR) therapy for treatment of liver metastases: measurement of response rate. *Journal of Surgical Oncology* **42**, 192-196. [insufficient clinical data]

Gray, B.N., Burton, M.A., Kelleher, D., Klemp, P. and Matz, L. (1990) Tolerance of the liver to the effects of Yttrium-90 radiation. *International Journal of Radiation Oncology, Biology, Physics* **18**, 619-623. [less than 10 patients]

Gullberg, G.T., Huesman, R.H., Malko, J.A., Pelc, N.J. and Budinger, T.F. (1985) An attenuated projector-backprojector for iterative SPECT reconstruction. *Physics in Medicine & Biology* **30**, 799-816. [not selective internal radiation therapy]

Ho, S., Lau, W.Y., Leung, T.W., Chan, M., Ngar, Y.K., Johnson, P.J. and Li, A.K. (1996) Partition model for estimating radiation doses from yttrium-90 microspheres in treating hepatic tumours. *European Journal of Nuclear Medicine* **23**, 947-952. [no clinical data]

Ho, S., Lau, W.Y. and Leung, W.T. (1997) Ultrasound guided internal radiotherapy using yttrium-90 glass microspheres for liver malignancies. *Journal of Nuclear Medicine* **38**, 1169-1170. [letter, no clinical data]

Ho, S., Lau, W.Y., Leung, T.W., Chan, M., Chan, K.W., Lee, W.Y., Johnson, P.J. and Li, A.K. (1997) Tumour-to-normal uptake ratio of 90Y microspheres in hepatic cancer

assessed with 99Tcm macroaggregated albumin. *British Journal of Radiology* **70**, 823-828. [technical paper, no clinical data]

Ho, S., Lau, W.Y., Leung, T.W. and Johnson, P.J. (1998) Internal radiation therapy for patients with primary or metastatic hepatic cancer: a review. *Cancer* **83**, 1894-1907. [review]

Ho, S., Johnson, P.J., Leung, W.T. and Lau, W.Y. (1999) Combating hepatocellular carcinoma with an integrated approach. *Chinese Medical Journal (English Edition)* **112**, 80-83. [review]

Houle, S., Yip, T.K., Shepherd, F.A., Rotstein, L.E., Sniderman, K.W., Theis, E., Cawthorn, R.H. and Richmond-Cox, K. (1989) Hepatocellular carcinoma: pilot trial of treatment with Y-90 microspheres. *Radiology* **172**, 857-860. [less than 10 patients]

Huang J.-F., Liang L.-J. and Yin X.-Y. (2000) Hepatic arterial infusion of 32P-glass microspheres (32P-GMS) in the treatment of unresected primary liver carcinoma. *Asian Journal of Surgery* **23**, 80-85. [not yttrium-90 microspheres]

Johnson, P.J. (1998) New treatment for hepatocellular carcinoma. *Journal of Gastroenterology and Hepatology* **13**, S311-S314 [review]

Lau, W.Y., Leung, T.W., Ho, S., Chan, M., Leung, N.W., Lin, J., Metreweli, C. and Li, A.K. (1994) Diagnostic pharmaco-scintigraphy with hepatic intra-arterial technetium-99m macroaggregated albumin in the determination of tumour to non-tumour uptake ratio in hepatocellular carcinoma. *British Journal of Radiology* **67**, 136-139. [technical paper, no clinical data]

Lau, W.Y., Leung, W.T., Ho, S., Leung, N.W., Chan, M., Lin, J., Metreweli, C., Johnson, P. and Li, A.K. (1994) Treatment of inoperable hepatocellular carcinoma with intrahepatic arterial yttrium-90 microspheres: a phase I and II study. *British Journal of Cancer* **70**, 994-999. [same patients are reported in Ho et al, 1997, Group1]

Leung, T.W., Lau, W.Y., Ho, S.K., Ward, S.C., Chow, J.H., Chan, M.S., Metreweli, C., Johnson, P.J. and Li, A.K. (1995) Radiation pneumonitis after selective internal radiation treatment with intraarterial 90yttrium-microspheres for inoperable hepatic tumors. *International Journal of Radiation Oncology, Biology, Physics* **33**, 919-924. [same patients are reported in Ho et al, 1997]

Lin, M. (1994) Radiation pneumonitis caused by yttrium-90 microspheres: Radiologic findings. *AJR.American Journal of Roentgenology* **162**, 1300-1302. [less than 10 patients]

Mantravadi, R.V., Spigos, D.G., Tan, W.S. and Felix, E.L. (1982) Intraarterial yttrium 90 in the treatment of hepatic malignancy. *Radiology* **142**, 783-786. [insufficient clinical data]

Marn, C.S., Andrews, J.C., Francis, I.R., Hollett, M.D., Walker, S.C. and Ensminger, W.D. (1993) Hepatic parenchymal changes after intraarterial Y-90 therapy: CT findings. *Radiology* **187**, 125-128. [same patients are reported in Andrews et al, 1994]

Moroz P. and Gray, B.N. (2000) Radiotherapy in the treatment of advanced liver cancer: Current status and future directions. *Asian Journal of Surgery* **23**, 32-41. [review]

Novell, J.R., Hilson, A. and Hobbs, K.E. (1991) Therapeutic aspects of radio-isotopes in hepatobiliary malignancy. *British Journal of Surgery* **78**, 901-906. [review]

Shepherd, F.A., Rotstein, L.E., Houle, S., Yip, T.C., Paul, K. and Sniderman, K.W. (1992) A phase I dose escalation trial of yttrium-90 microspheres in the treatment of primary hepatocellular carcinoma. *Cancer* **70**, 2250-2254. [not liver metastases, not SIR-Spheres]

Stribley, K.V., Gray, B.N., Chmiel, R.L., Heggie, J.C. and Bennett, R.C. (1983) Internal radiotherapy for hepatic metastases II: The blood supply to hepatic metastases. *Journal of Surgical Research* **34**, 25-32. [review]

Stubbs, R.S. and Cannan, R.J. (1999) Active treatment of colorectal hepatic metastases. *New Zealand Family Physician* **August 1999**. [insufficient clinical data, additional clinical data on 50 patients is reported in Stubbs et al, 2001]

Stubbs, R.S., Cannan, R.J., Mitchell, A.W. and Alwan, M.H. (2000) An initial experience with selective internal radiation therapy (SIRT) for non-resectable colorectal liver metastases. *GI Cancer* **3**, 135-143.[additional clinical data on 50 patients is reported in Stubbs et al, 2001]

Tian, J.H., Xu, B.X., Zhang, J.M., Dong, B.W., Liang, P. and Wang, X.D. (1996) Ultrasound-guided internal radiotherapy using yttrium-90-glass microspheres for liver malignancies [see comments]. *Journal of Nuclear Medicine* **37**, 958-963. [not liver metastases, not SIR-Spheres]

Vergote, I., Larsen, R.H., De Vos, L., Winderen, M., Ellingsen, T., Bjorgum, J., Hoff, P., Aas, M. and Nustad, C.T.K. (1992) Distribution of intraperitoneally injected microspheres labeled with the alpha-emitter astatine-211 compared with phosphorus-32 and yttrium-90 colloids in mice. *Gynecologic Oncology* **47**, 358-365. [animal data only]

Wickremesekera, J.K., Cannan, R.J. and Stubbs, R.S. (2000) Hepatic artery access ports: recognizing and avoiding the problems. *Australian & New Zealand Journal of Surgery* **70**, 496-502. [technical paper, no clinical data]

Wike, J.S., Guyer, C.E., Ramey, D.W. and Phillips, B.P. (1990) Chemistry for commercial scale production of yttrium-90 for medical research. *Applied Radiation & Isotopes* **41**, 861-865. [technical paper, no clinical data]

Wollner, I.S., Knutsen, C.A., Ullrich, K.A., Chrisp, C.E., Juni, J.E., Andrews, J.C., Tuscan, M.J., Stetson, P.L. and Ensminger, W.D. (1987) Effects of hepatic arterial yttrium-90 microsphere administration alone and combined with regional bromodeoxyuridine infusion in dogs. *Cancer Research* **47**, 3285-3290. [animal data only]

Yan, Z.P., Lin, G., Zhao, H.Y. and Dong, Y.H. (1993) An experimental study and clinical pilot trials on yttrium-90 glass microspheres through the hepatic artery for treatment of primary liver cancer. *Cancer* **72**, 3210-3215.[not liver metastases, not SIR-Spheres]

Yorke, E.D., Jackson, A., Fox, R.A., Wessels, B.W. and Gray, B.N. (1999) Can current models explain the lack of liver complications in Y-90 microsphere therapy? *Clinical Cancer Research* **5**, 3024s-3030s. [model, no clinical data]

Yu, L. (1994) Experimental treatment of liver cancer with Yttrium-90 glass microspheres. *Chinese Journal of Clinical Oncology* **21**, 861-864. [animal data only]

Zavgorodni, S.F. (1996) A model for dose estimation in therapy of liver with intraarterial microspheres. *Physics in Medicine & Biology* **41**, 2463-2480. [model, no clinical data]

Appendix E Calculations

Tables 36, 37 (original analysis) and 38 (re-analysis) show the calculations of tumour response in the HAC plus SIRT versus HAC alone trial. Tumour response is calculated based on the conventional measure of patients with complete or partial response to therapy (CR or PR). Data are from the original analysis, where the primary investigator assessed tumour response and the re-analysis, where a blinded independent reader conducted the assessment of tumour response.

Table 36 Original analysis of tumour response - measured by tumour volume

Response	HAC	HAC + SIRT
	n = 35	n = 39
CR	1	2
PR	7	16
NC	12	12
PD	9	6
Other	6	3
Responders CR + PR	8	18
Proportion of responders	0.23	0.46
Difference in proportions	0.23	
95% Confidence Interval around difference	0 – 0.43	
p (Fisher's exact test)	0.06	

CR – complete response; PR – partial response; NC – no change; PD – progressive disease

Table 37 Original analysis of tumour response - measured by tumour area

Response	HAC	HAC + SIRT
	n = 35	n = 39
CR	0	2
PR	6	14
NC	13	15
PD	8	4
Other	8	4
Responders CR + PR	6	16
Proportion of responders	0.17	0.41
Difference in proportions	0.24	
95% Confidence Interval around difference	0.04 – 0.45	
p (Fisher's exact test)	0.04	

CR – complete response; PR – partial response; NC – no change; PD – progressive disease

Table 38 Re-analysis of tumour response by blinded independent reader- measured by tumour area

Response	HAC	HAC + SIRT
	n = 35	n = 39
CR	1	2
PR	7	16
NC	11	12
PD	10	6
Other	6	3
Responders CR + PR	8	18
Proportion of responders	0.23	0.46
Difference in proportions	0.23	
95% Confidence Interval around difference	0.01 – 0.43	
p (Fisher's exact test)	0.05	

CR – complete response; PR – partial response; NC – no change; PD – progressive disease

Appendix F RECIST criteria

RECIST criteria (Response Evaluation Criteria in Solid Tumours) have been developed as a result of a large international collaboration of the European Organization for Research and Treatment of Cancer (EORTC), the National Cancer Institute (NCI) of the United States and the National Cancer Institute of Canada Clinical Trials Group.

The RECIST process and recommendations are reported extensively in Therasse et al (2000). They include comment on the following areas:

- Measurability of Tumour Lesions at Baseline, including definitions and specifications by different types of measurement (including clinical examination, imaging, tumour markers and histology)

- Tumour Response Evaluation, including baseline evaluation, response criteria (target lesions, non-target lesions, best overall response, frequency of re-evaluation, confirmation, duration of overall response or stable disease), progression-free survival / time to progression

- Response Review

- Reporting of Results

- Response Evaluation in Randomised Phase III trials

The specific areas of the document that are applicable to results reported for SIRT are described below.

'**3.2.3 Evaluation of best overall response**. The best overall response is the best response recorded from the start of treatment until disease progression/recurrence occurs (taking as reference for progressive disease the smallest measurements recorded since treatment started. In general, the patient's best response assignment will depend upon the achievement of both measurement and confirmation criteria.'

Table 39 Overall responses for all possible combinations of tumour responses in target and nontarget lesions with or without the appearance of new lesions

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response / SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

'**3.3.1 Confirmation.** The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. This aspect of response evaluation is particularly important in nonrandomized trials where response is the primary end point. In this setting, to be assigned a status of partial response or complete response, changes in tumour measurements must be confirmed by repeat assessments

that should be performed no less than 4 weeks after the criteria for response are first met. …In the case of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general not less than 6-8 weeks) that is defined in the study protocol. Repeat studies to confirm changes in tumour size may not always be feasible or may not be part of the standard practice in protocols where progression free or overall survival are the key endpoints. In such cases patients will not have a 'confirmed response'. This distinction should be made clear when reporting the outcome of such studies…'

Table 40 Comparison of WHO and RECIST guidelines

Characteristic	WHO	RECIST
Measurability of lesions at baseline	**Measurable disease** Bidimensional (product of longest diameter (LD) and greatest perpendicular diameter)§	**Measurable disease** Unidimensional (longest diameter (LD) only, size with conventional techniques > 20mm; spiral CT > 10mm)
	Nonmeasurable/evaluable disease eg lymphangitic pulmonary metastases, abdominal masses)	Nonmeasurable disease all other lesions, including small lesions. Evaluable is not recommended
Objective response	**Measurable disease** Change in sum of products of LDs and greatest perpendicular diameters, no maximum number of lesions specified	**Target lesions** Change in sum of LDs, maximum of 5 per organ up to 10 total [more than one organ])
	CR: disappearance of all known disease, confirmed at ≥ 4 weeks	CR: disappearance of all target lesions, confirmed at ≥ 4 weeks
	PR: ≥ 50% decrease from baseline, confirmed at ≥ 4 weeks	PR: ≥ 30% decrease from baseline, confirmed at ≥ 4 weeks
	PD: ≥ 25% increase of one or more lesions, or appearance of new lesions	PD: ≥ 20% increase over smallest sum observed, or appearance of new lesions
	NC: neither PR or PD criteria met	SD: neither PR or PD criteria met
	Non measurable disease CR: disappearance of all known disease, confirmed at ≥ 4 weeks	**Nontarget lesions** CR: disappearance of all target lesions and normalisation of tumour markers, confirmed at ≥ 4 weeks
	PR: estimated decrease of ≥ 50%, confirmed at ≥ 4 weeks	
	PD: estimated increase of ≥ 25% in existent lesions, or appearance of new lesions	PD: unequivocal progression of nontarget lesions, or appearance of new lesions
	NC: neither PR or PD criteria met	Non-PD: persistence of one or more nontarget lesions and/or tumour markers above normal limits
Overall response	Best response recorded in measurable disease	Best response recorded in measurable disease from treatment start to disease progression or recurrence
	NC in nonmeasurable lesions will reduce a CR in measurable lesions to an overall PR	Non-PD in nontarget lesion(s) will reduce a CR in target lesions(s) to an overall PR
	NC in nonmeasurable lesions will not reduce a PR in measurable lesions	Non-PD in nontarget lesion(s) will not reduce a PR in target lesion(s)
Duration of response	CR From: date CR criteria first met To: date PD first noted	Overall CR From: date CR criteria first met To: date recurrent disease first noted
	Overall response From: date of treatment start To: date PD first noted	Overall response From: date CR or PR criteria first met (whichever status cane first) To: date recurrent disease or PD first noted
	In patients who only achieve a PR, only the period of overall response should be recorded	SD From: date of treatment start To: date PD first noted

From (Gehan & Tefft 2000)

LD = longest diameter, CR = complete response, PR = partial response, PD = progressive disease, NC = no change, SD = stable disease

§ lesions that can only be measured unidimensionally are considered to be measurable (eg mediastinal adenopathy, malignant hepatomegaly)

Abbreviations

5-FU	5-flourouracil
AST	aspartate amino-transferase
CEA	carcinoembryonic antigen
CR	complete response
CRC	colorectal cancer
CT	computed tomography
FLIC	Functional Living Index - Cancer
FUDR	floxuridine
GI	gastrointestinal
HAC	hepatic arterial chemotherapy
ICER	incremental cost effectiveness ratio
ITT	intention-to-treat
LM	liver metastases
LV	leucovorin
LYS	life year saved
MAA	macroaggregated albumin
MERGE	Method for Evaluating Research Guideline Evidence
n/a	not applicable
NC	no change
PD	progressive disease
PLC	primary liver cancer
PR	partial response
PT	pre-treatment
pts	patients
QALY	quality-adjusted life year
QOL	quality of life
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SD	stable disease
SIR-Spheres	Selective Internal Radiotherapy-Spheres
SIRT	Selective Internal Radiation Therapy
UICC	Union Internationale Contre le Cancer

References

Advanced Colorectal Cancer Meta-analysis Project 1992, "Modulation of fluorouracil by leukovorin in patients with advanced colorectal cancer: evidence in terms of response rate", *Journal of Clinical Oncology*, vol. 10, pp. 896-903.

Allen-Mersh, T., Glover, C., Fordy, C., Mathur, P., & Quinn, H. 2000, "Randomized trail of regional plus systematic fluorinated pyrimidine compared with systemic fluorinated pyrimidine in treatment of colorectal liver metastases", *European Journal of Surgical Oncology*, vol. 26, no. 5, pp. 468-473.

Allen-Mersh, T. G., Earlam, S., & Fordy, C. 1994, "Quality of life and survival with continuous hepatic artery floxuridine infusion for colorectal liver metastases", *Lancet*, vol. 344, pp. 1255-1260.

Amin, Z., Bown, S. G., & Less, W. R. 1993, "Local treatment of colorectal liver metastases: a comparison of interstitial laser photocoagulation (ILP) and percutaneous ethanol (PAI)", *Clinical Radiology*, vol. 48, pp. 166-171.

Andrews, J. C., Walker, S. C., Ackermann, R. J., Cotton, L. A., Ensminger, W. D., & Shapiro, B. 1994a, "Hepatic radioembolization with yttrium-90 containing glass microspheres: preliminary results and clinical follow-up", *Journal of Nuclear Medicine*, vol. 35, no. 10, pp. 1637-1644.

Australian Institute of Health and Welfare & Australasian Association of Cancer Registries 2000, *Cancer in Australia 1997: Incidence and Mortality Data for 1997 and selected data for 1998 and 1999*, Australian Institute of Health and Welfare, Canberra.

Bines, S. D., Doolas, A., Jenkins L., & et al 1996, "Survival after repeat hepatic resection for recurrent colorectal hepatic metastases", *Surgery*, vol. 120, pp. 591-596.

Blanchard, R. J., Morrow, I. M., & Sutherland, J. B. 1989b, "Treatment of liver tumors with yttrium-90 microspheres alone", *Canadian Association of Radiologists Journal*, vol. 40, no. 4, pp. 206-210.

Clinical Oncology Society of Australia & Australian Cancer Network 1999, *The prevention, early detection and management of colorectal cancer* Canberra.

Commonwealth Department of Health and Aged Care. Medicare Benefits Schedule, November 1, 2000. DHAC Available from: http://www.health.gov.au/pubs/mbs/mbs6/default.htm. 2000a.

Commonwealth Department of Health and Aged Care, A. a. C. C. B. 2000b, *Australian hospital morbidity data, AR-DRG v4.0 February 3 2000. Available from: http://www.health.gov.au:80/casemix/report/hospmo10.htm.*

Commonwealth Department of Health and Aged Care, A. a. C. C. B. 2001, *1999-2000 Australian Hospital Morbidity Data. AR-DRG v4.1. October 22 2001. Available from: http://www.health.gov.au:80/casemix/report/hospmo21.htm#Diagnoses.*

Gehan, E. A. & Tefft, M. C. 2000, "Will there be resistance to RECIST (Response Evaluation Criteria in Solid Tumors)?", *Journal of the National Cancer Institute*, vol. 92, no. 3, pp. 179-181.

Giovanni, M. & Seitz, U. F. 1994, "Ultrasound guided percutaneous injection of small liver metastases", *Cancer*, vol. 73, pp. 294-297.

Grady, E. D., McLaren, J., Auda, S. P., & McGinley, P. H. 1983c, "Combination of internal radiation therapy and hyperthermia to treat liver cancer", *Southern Medical Journal*, vol. 76, no. 9, pp. 1101-1105.

Gray, B., van Hazel, G., Blackwell, A., Anderson, J., Price, D., Moroz, P., Bower, G., & Jackson, L. 2001d, "Randomised Phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy *versus* fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer (submitted)", *Journal of Clinical Oncology*, vol. (submitted only).

Gray, B., van Hazel, G., Hope, M., Burton, M. A., Moroz P., Paton, G., & Anderson, J. 2000a, "Randomised trial of SIR-Spheres plus chemotherapy versus chemotherapy alone for treating patients with liver metastases from primary large bowel cancer (Submitted)", *Journal of Clinical Oncology*, vol. (Submitted only).

Gray, B. N., Anderson, J. E., Burton, M. A., van Hazel, G., Codde, J., Morgan, C., & Klemp, P. 1992f, "Regression of liver metastases following treatment with yttrium-90 microspheres", *Australian & New Zealand Journal of Surgery*, vol. 62, no. 2, pp. 105-110.

Gray, B. N., van Hazel, G., Buck, M., Paton, G., Burton, M. A., & Anderson, J. 2000b, "Treatment of colorectal liver metastases with SIR-spheres plus chemotherapy", *GI Cancer*, vol. 3, no. 4, pp. 249-257.

Gray, R. J. 1988, "A class of k-sample tests for comparing the cumulative incidence of a competing risk", *Annals of Statistics* pp. 1141-1154.

Herba, M. J., Illescas, F. F., Thirlwell, M. P., Boos, G. J., Rosenthall, L., Atri, M., & Bret, P. M. 1988h, "Hepatic malignancies: improved treatment with intraarterial Y-90", *Radiology*, vol. 169, no. 2, pp. 311-314.

Ho, S., Lau, W. Y., Leung, T. W., Chan, M., Johnson, P. J., & Li, A. K. 1997i, "Clinical evaluation of the partition model for estimating radiation doses from yttrium-90 microspheres in the treatment of hepatic cancer", *European Journal of Nuclear Medicine*, vol. 24, no. 3, pp. 293-298.

Hohn, D. C., Stagg, R. J., Friedman, M. A., & et al 1989, "A randomized trial of continuous intravenous versus hepatic intrarterial floxuridine in patients with colorectal cancer metastatic to the liver: the Northern California Oncology Group Trial", *Journal of Clinical Oncology*, vol. 7, pp. 1646-1654.

Hughes, K. S., Rosenstein, R. B., Songhorabodi, S., & et al 1988, "Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of long-term survivors", *Disease of the Colon and Rectum*, vol. 31, pp. 1-4.

Kemeny, N., Daly, J., Reichman, B., & et al 1987, "Intrahepatic or systemic infusion of fluourodeoxyuridine in patients with liver metastases from colorectal carcinoma. A randomized trial", *Annals of International Medicine*, vol. 107, pp. 459-465.

Kemeny, N., Huang, Y., Cohen, A. M., Shi, W., Conti, J. A., Brennan, M. F., Bertino, J. R., Turnbull, A. D. M., Sullivan, D., Stockman, J., Blumgart, L. H., & Fong, Y. 1999, "Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer", *New England Journal of Medicine*, vol. 341, no. 27, pp. 2039-2048.

Korpan, N. N. 1997, "Hepatic cryosurgery for liver metastases. Long term follow up", *Annals of Surgery*, vol. 225, pp. 193-201.

Lau, W. Y., Ho, S., Leung, T. W., Chan, M., Ho, R., Johnson, P. J., & Li, A. K. 1998j, "Selective internal radiation therapy for nonresectable hepatocellular carcinoma with intraarterial infusion of 90yttrium microspheres", *International Journal of Radiation Oncology, Biology, Physics*, vol. 40, no. 3, pp. 583-592.

Liddle, J., Williamson, M., & Irwig, L. 1996, *Method for evaluating research guideline evidence*, NSW Department of Health, Sydney.

Loeffler, T., Korsten, F. W., Reis, H. E., & et al 1992, "Fluorouracil as monotherapy or combined with folinic acid in the treatment of metastasizing colorectal carcinoma", *Deutsche Medizinische Wochenschrift*, vol. 117, pp. 1007-1013.

Lorenz, M. & Muller, H.-H. 2000, "Randomized, multicenter trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus flurodesoxyuridine administered via hepatic arterial infusion in patients with nonresectable liver metastases from colorectal cancer", *Journal of Clinical Oncology*, vol. 18, no. 2, pp. 243-254.

Martin, J. K., O'Connell, M. J., Wieand, H. S., & et al 1990, "Intra-arterial floxuridine vs systemic fluorouracil for hepatic metastases from colorectal cancer", *Archives of Surgery*, vol. 125, pp. 1022-1027.

Meta-analysis Group in Cancer 1996, "Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer", *Journal of the National Cancer Institute*, vol. 88, pp. 252-258.

Morris, D. L., Ross, W. B., Iqbal, J., & et al 1996, "Cryoablation of hepatic malignancy: and evaluation of tumor marker data and survival in 110 patients", *GI Cancer*, vol. 1, pp. 247-251.

National Health and Medical Research Council 1984, *Administration of ionising radiation to human subjects in medical research*, Australian Government Publishing Service, Canberra, 12.

National Health Service 1997, *Improving outcomes in colorectal cancer: research evidence*., National Health Service, United Kingdom, 97CC 01200.

National Occupational Health and Safety Commission 1995, *Recommendations for limiting exposure to ionizing radiation [NOHSC:3022] and National Standard for Limiting Occupational Exposure to Ionizing Radiation [NOHSC 1013]*, Australian Government Publishing Service, Canberra, 39.

Nordic Gastrointestinal Tumour Adjuvant Therapy Group 1992, "Expectant or primary chemotherapy in patients with advanced symptomatic colorectal cancer: a randomised trial", *Journal of Clinical Oncology*, vol. 10, pp. 904-911.

Onik, G., Atkinson, D., Zemel, R., & Weaver, L. 1993, "Cryosurgery of liver cancer", *Surgical Oncology*, vol. 9, pp. 309-317.

Onik, G., Rubinsky, B., Zemel, R., & et al 1991, "Ultrasound-guided hepatic cryosurgergy in the treatment of metastatic colon carcinoma - preliminary results", *Cancer*, vol. 67, pp. 901-907.

Petrioli, R., Lorenzi, M., Aquino, A., & et al 1995, "Treatment of advanced colorectal cancer with high dose-intensity folinic acid and fluorouracil plus suppotive care", *European Journal of Cancer*, vol. 3, pp. 2105-2108.

Rougier, P., Paillot, B., LaPlanche, A., & et al 1997, "5-Fluorouracil (5FU) continuous intravenous infusion compared with bolus administration. Final results of a randomised trial in metastatic colorectal cancer", *European Journal of Cancer*, vol. 33, pp. 1789-1793.

Seifert, J. K. & Morris, D. L. 1999, "A world survey on the complications of hepatic and prostate cryotherapy", *World Journal of Surgery*, vol. 23, no. 2, pp. 109-113.

Shafir, M., Shapiro, R., Sung, M., & et al 1996, "Cryoablation of unresectable malignant liver tumours", *American Journal of Surgery*, vol. 171, pp. 27-31.

Shepherd, F. A., Rotstein, L. E., Houle, S., Yip, T. C., Paul, K., & Sniderman, K. W. 1992, "A phase I dose escalation trial of yttrium-90 microspheres in the treatment of primary hepatocellular carcinoma", *Cancer*, vol. 70, no. 9, pp. 2250-2254.

SIRTeX Medical Ltd. SIR-Spheres Physician and Institution Labeling (available from www.sirtex.com/pdf/physician.pdf). 2000a.

SIRTeX Medical Ltd. SIR-Spheres Product Monograph (available from www.sirtex.com/pdf/monograph.pdf). 2000b.

SIRTeX Medical Ltd. SIRTeX Medical Ltd Submission to MSAC for Selective Internal Radiotherapy using SIR-Spheres (MSAC Application 1034). 2000c.

SIRTeX Medical Ltd. SIRTeX Medical Ltd. Company Website (www.sirtex.com). 2001.

Stubbs, R. S., Cannan, R. J., & Mitchell, A. W. 2001, "Selective internal radiation therapy with 90Yttrium microspheres for extensive colorectal liver metastases", *Journal of Gastrointestinal Surgery*, vol. 5, no. 3, pp. 294-302.

Stubbs, R. S., Cannan, R. J., Mitchell, A. W., & Alwan, M. H. 2000k, "An initial experience with selective internal radiation therapy (SIRT) for non-resectable colorectal liver metastases", *GI Cancer*, vol. 3, no. 2, pp. 135-143.

Taylor, I. 1996, "Liver metastases from colorectal cancer: lessons from past and present clinical studies", *British Journal of Surgery*, vol. 83, no. 4, pp. 456-460.

Therasse, P., Arbuck, S., Eisenhauer, E., Wanders, J., Kaplan, R. S., Rubinstein, L., Verweij, J., Van Glabbeke, M., van Oosterom, A. T., Christian, M. C., & Gwyther, S. G.

2000, "New guidelines to evaluate the response to treatment in solid tumours", *Journal of the National Cancer Institute*, vol. 92, pp. 205-216.

Vauthey, J.N., Marsh, R. D., Cendan, J. C., Chu, N.-M., & Copeland, E. M. 1996, "Arterial therapy of hepatic colorectal metastases", *British Journal of Surgery*, vol. 83, no. 4, pp. 447-455.

Vogl, T. J., Mack, M. G., Straub, R., & et al 1995, "Guided laser induced thermotherapy of liver metastases", *Radiology*, vol. 35, pp. 188-199.

Weaver, M. L., Atkinson, D., Zemel, R., & et al 1995, "Hepatic cryosurgery in the treatment of unresectable metastases", *Surgical Oncology*, vol. 4, pp. 231-236.

Webb, D. V., Solomon, S. B., & Thomson, J. E. M. 1999, "Background radiation levels and medical exposure levels in Australia", *Radiation Protection In Australia*, vol. July 16, pp. 25-32.

Wood, C. B., Gillis, C. R., Blumgart, L. H., & et al 1976, "A retrospective study of the natural history of patients with liver metastases from colorectal cancer", *Clinical Oncology*, vol. 2, pp. 285-288.

Yeh, K. E., Fortunato, L., Hoffman, J. P., & Eisenberg, B. L. 1997, "Cryoablation of hepatic metastases from colorectal carcinomas", *American Surgeon*, vol. 63, pp. 63-68.